

\$ * * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 14:09:47 ON 08 MAR 2004

=> fil .bec

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.48

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
ESBIOBASE, BIOTECHNO, WPIDS' ENTERED AT 14:10:56 ON 08 MAR 2004
ALL COPYRIGHTS AND RESTRICTIONS APPLY. SEE HELP USAGETERMS FOR DETAILS.

11 FILES IN THE FILE LIST

=> s thymosin(2a)beta

FILE 'MEDLINE'

1774 THYMOSIN

474506 BETA

L1 373 THYMOSIN(2A)BETA

FILE 'SCISEARCH'

1525 THYMOSIN

631186 BETA

L2 456 THYMOSIN(2A)BETA

FILE 'LIFESCI'

434 THYMOSIN

152382 BETA

L3 127 THYMOSIN(2A)BETA

FILE 'BIOTECHDS'

87 THYMOSIN

36229 BETA

L4 24 THYMOSIN(2A)BETA

FILE 'BIOSIS'

2118 THYMOSIN

627134 BETA

L5 529 THYMOSIN(2A)BETA

FILE 'EMBASE'

1951 THYMOSIN

530227 BETA

L6 320 THYMOSIN(2A)BETA

FILE 'HCAPLUS'

1929 THYMOSIN

1240967 BETA

L7 645 THYMOSIN(2A)BETA

FILE 'NTIS'

15 THYMOSIN

20098 BETA

L8 1 THYMOSIN(2A)BETA

FILE 'ESBIOBASE'

265 THYMOSIN

185235 BETA

L9 153 THYMOSIN(2A)BETA

FILE 'BIOTECHNO'

549 THYMOSIN

185944 BETA

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L10      189 THYMOSIN(2A)BETA

FILE 'WPIDS'
      233 THYMOSIN
      107193 BETA
L11      48 THYMOSIN(2A)BETA

TOTAL FOR ALL FILES
L12      2865 THYMOSIN(2A) BETA

=> s l12(5a)gene/q
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L13      50 L1 (5A)GENE/Q

FILE 'SCISEARCH'
L14      50 L2 (5A)GENE/Q

FILE 'LIFESCI'
L15      31 L3 (5A)GENE/Q

FILE 'BIOTECHDS'
L16      12 L4 (5A)GENE/Q

FILE 'BIOSIS'
L17      97 L5 (5A)GENE/Q

FILE 'EMBASE'
L18      53 L6 (5A)GENE/Q

FILE 'HCAPLUS'
L19      227 L7 (5A)GENE/Q

FILE 'NTIS'
L20      0 L8 (5A)GENE/Q

FILE 'ESBIOBASE'
L21      21 L9 (5A)GENE/Q

FILE 'BIOTECHNO'
L22      47 L10(5A)GENE/Q

FILE 'WPIDS'
L23      13 L11(5A)GENE/Q

TOTAL FOR ALL FILES
L24      601 L12(5A) GENE/Q

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      1681201 2001-2004/PY
L25      42 L13 NOT 2001-2004/PY

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L26      40 L14 NOT 2001-2004/PY

FILE 'LIFESCI'
      299805 2001-2004/PY
L27      25 L15 NOT 2001-2004/PY

FILE 'BIOTECHDS'
      65455 2001-2004/PY
L28      7 L16 NOT 2001-2004/PY

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FILE 'BIOSIS'
1652044 2001-2004/PY
L29 67 L17 NOT 2001-2004/PY

FILE 'EMBASE'
1431975 2001-2004/PY
L30 39 L18 NOT 2001-2004/PY

FILE 'HCAPLUS'
3173103 2001-2004/PY
L31 107 L19 NOT 2001-2004/PY

FILE 'NTIS'
44760 2001-2004/PY
L32 0 L20 NOT 2001-2004/PY

FILE 'ESBIOBASE'
894776 2001-2004/PY
L33 10 L21 NOT 2001-2004/PY

FILE 'BIOTECHNO'
368875 2001-2004/PY
L34 33 L22 NOT 2001-2004/PY

FILE 'WPIDS'
3008836 2001-2004/PY
L35 1 L23 NOT 2001-2004/PY

TOTAL FOR ALL FILES
L36 371 L24 NOT 2001-2004/PY

=> fil .becpat
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
25.28	25.76

FULL ESTIMATED COST

FILES 'BIOTECHDS, HCAPLUS, WPIDS' ENTERED AT 14:19:22 ON 08 MAR 2004
ALL COPYRIGHTS AND RESTRICTIONS APPLY. SEE HELP USAGETERMS FOR DETAILS.

3 FILES IN THE FILE LIST

=> s l24 and wo/pc and pry=<2000 range=2003,
FILE 'BIOTECHDS'

10186 WO/PC
3567 PRY=<2000
(PRY=<2000)
L37 0 L16 AND WO/PC AND PRY=<2000

FILE 'HCAPLUS'
62180 WO/PC
25885 PRY=<2000
L38 2 L19 AND WO/PC AND PRY=<2000

FILE 'WPIDS'
139623 WO/PC
133446 PRY=<2000
(PRY=<2000)
L39 0 L23 AND WO/PC AND PRY=<2000

TOTAL FOR ALL FILES
L40 2 L24 AND WO/PC AND PRY=<2000

=> d tot

L40 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
 TI Sequence homologs of human thymosin, ephrin A receptors, and fibromodulin,
 and their therapeutic application
 SO U.S. Pat. Appl. Publ., 88 pp., Cont.-in-part of U.S. Ser. No.
 20,00,687,276.
 CODEN: USXXCO

IN Prayaga, Sudhirdas K.; Taupier, Raymond J.; Bandaru, Raj
 AN 2003:855542 HCAPLUS
 DN 139:359914

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2003203426	A1	20031030	US 2001-973424	20011009	<--
	WO 2002030979	A2	20020418	WO 2001-US31498	20011010	<--
	WO 2002030979	A3	20030619			
	W:					
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,					
	CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,					
	GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,					
	LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,					
	PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,					
	US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW:					
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,					
	DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,					
	BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
	AU 2002011543	A5	20020422	AU 2002-11543	20011010	<--

L40 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
 TI Sequence homologs of proteins associated with regulation of cell growth
 and adhesion and cDNAs encoding them and their possible uses
 SO U.S. Pat. Appl. Publ., 179 pp., Cont.-in-part of U.S. Ser. No. 540,763.
 CODEN: USXXCO

IN Spytek, Kimberly A.; Majumder, Kumud; Tchernev, Velizar T.; Mishra,
 Vishnu; Padigar, Muralidhara; Spaderna, Steven K.; Shenoy, Suresh G.;
 Rastelli, Luca; Li, Li; Taupier, Raymond J.; Gangolli, Esha
 AN 2003:836486 HCAPLUS
 DN 139:318461

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	US 2003198953	A1	20031023	US 2001-863776	20010523	<--
	AU 2001069710	A5	20011203	AU 2001-69710	20010523	<--
	WO 2001090155	A2	20011129	WO 2001-US17073	20010524	<--
	WO 2001090155	A3	20031002			
	W:					
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	HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,					
	LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,					
	RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,					
	VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
	RW:					
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,					
	DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,					
	BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
	EP 1364014	A2	20031126	EP 2001-948241	20010524	<--
	R:					
	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,					
	IE, FI, CY, TR					

=> log y

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

19.58

45.34

STN INTERNATIONAL LOGOFF AT 14:24:13 ON 08 MAR 2004

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1083	thymosin	US-PGPUB; USPAT	OR	OFF	2004/03/08 14:50
L2	93	1 near5 (gene\$1 or sequence\$1)	US-PGPUB; USPAT	OR	OFF	2004/03/08 14:51
L3	148	1 adj beta	US-PGPUB; USPAT	OR	OFF	2004/03/08 14:51
(L4)	26	2 and 3	US-PGPUB; USPAT	OR	OFF	2004/03/08 14:51

PGPUB-DOCUMENT-NUMBER: 20040029220

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040029220 A1

TITLE: Novel proteins and nucleic acids encoding same

PUBLICATION-DATE: February 12, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Vernet, Corine A.M.	North Branford	CT	US	
Fernandes, Elma R.	Branford	CT	US	
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Li, Li	Branford	CT	US	
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APPL-NO: 10/ 174333

DATE FILED: June 18, 2002

RELATED-US-APPL-DATA:

child 10174333 A1 20020618

parent continuation-in-part-of 09842758 20010425 US PENDING

non-provisional-of-provisional 60298994 20010618 US

non-provisional-of-provisional 60386837 20020607 US

non-provisional-of-provisional 60200158 20000426 US

non-provisional-of-provisional 60200613 20000428 US

non-provisional-of-provisional 60200780 20000428 US

non-provisional-of-provisional 60201006 20000501 US
non-provisional-of-provisional 60201007 20000501 US
non-provisional-of-provisional 60201236 20000501 US
non-provisional-of-provisional 60201238 20000501 US
non-provisional-of-provisional 60201186 20000502 US
non-provisional-of-provisional 60201474 20000503 US
non-provisional-of-provisional 60201508 20000503 US
non-provisional-of-provisional 60220591 20000725 US
non-provisional-of-provisional 60232678 20000915 US
non-provisional-of-provisional 60263217 20010122 US
non-provisional-of-provisional 60265160 20010130 US
non-provisional-of-provisional 60269531 20010216 US

US-CL-CURRENT: 435/69.1, 435/320.1 , 435/325 , 530/350 , 536/23.2

ABSTRACT:

Disclosed herein are nucleic acid sequences that encode G-coupled protein-receptor related polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

RELATED APPLICATIONS

[0001] This application claims priority from U.S. Ser. No. 60/298,994, filed on Jun. 18, 2001; U.S. Ser. No. _____, filed on Jun. 7, 2002; and U.S. Ser. No. 09/842,758, filed on Apr. 25, 2001, which claims priority from U.S. Ser. No. 60/200,158, filed Apr. 26, 2000; U.S. Ser. No. 60/200,613, filed Apr. 28, 2000; U.S. Ser. No. 60/200,780, filed Apr. 28, 2000; U.S. Ser. No. 60/201,006, filed May 1, 2000; U.S. Ser. No. 60/201,007, filed May 1, 2000; U.S. Ser. No. 60/201,236, filed May 1, 2000; U.S. Ser. No. 60/201,238, filed May 1, 2000; U.S. Ser. No. 60/201,186, filed May 2, 2000; U.S. Ser. No. 60/201,474, filed May 3, 2000; U.S. Ser. No. 60/201,508, filed on May 3, 2001; U.S. Ser. No. 60/220,591, filed on Jul. 25, 2000; U.S. Ser. No. 60/232,678 filed Sep. 15, 2000; U.S. Ser. No. 60/263,217 filed Jan. 22, 2001; U.S. Ser. No. 60/265,160, filed Jan. 30, 2001; and U.S. Ser. No. 60/269,531, filed Feb. 16, 2001, each of which is incorporated by reference in its entirety.

----- KWIC -----

Summary of Invention Paragraph - BSTX (233):

[0231] The full MOL5 amino acid sequence has 37 of 45 amino acid residues

(82%) identical to, and 38 of 45 residues (84%) positive with, the 45 amino acid residue Thymosin beta protein from Homo sapiens (ptnr: PIR-ID:JC5274) (E=1.2e.sup.-11).

Summary of Invention Paragraph - BSTX (236):

[0234] Thymosin-beta-4 induces the expression of terminal deoxynucleotidyl transferase activity in vivo and in vitro, inhibits the migration of macrophages, and stimulates the secretion of hypothalamic luteinizing hormone-releasing hormone. It was noted that the protein was originally isolated from a partially purified extract of calf thymus, thymosin fraction 5, which induced differentiation of T cells and was partially effective in some immuno-compromised animals. Further studies demonstrated that the molecule is ubiquitous; it had been found in all tissues and cell lines analyzed. It is found in highest concentrations in spleen, thymus, lung, and peritoneal macrophages. It was stated that thymosin-beta-4 is an actin monomer sequestering protein that may have a critical role in modulating the dynamics of actin polymerization and depolymerization in nonmuscle cells. Its regulatory role is consistent with the many examples of transcriptional regulation of T-beta-4 and of tissue-specific expression. Lymphocytes have a unique T-beta-4 transcript relative to the ubiquitous transcript found in many other tissues and cells. It was stated that rat thymosin-beta-4 is synthesized as a 44-amino acid propeptide which is processed into a 43-amino acid peptide by removal of the first methionyl residue. The molecule does not have a signal peptide. Human thymosin-beta-4 has a high degree of homology to rat thymosin-beta-4; the coding regions differ by only 9 nucleotides, and these are all silent base changes.

Summary of Invention Paragraph - BSTX (237):

[0235] By differential screening of a cDNA library prepared from leukocytes of an acute lymphocytic leukemia patient, a cDNA encoding thymosin-beta-4 was isolated. Using Northern blot analysis, the expression of the 830-nucleotide thymosin-beta-4 mRNA in various primary myeloid and lymphoid malignant cell lines and in hemopoietic cell lines was studied. It was stated that the pattern of thymosin-beta-4 gene expression suggests that it may be involved in an early phase of the host defense mechanism.

Summary of Invention Paragraph - BSTX (238):

[0236] A cDNA clone for the human interferon-inducible gene 6-26 was isolated and showed that its sequence was identical to that for the human thymosin-beta-4 gene. By use of a panel of human rodent somatic cell hybrids, it was shown that the 6-26 cDNA recognized seven genes, members of a multigene family, present on chromosomes 1, 2, 4, 9, 11, 20, and X. These genes are symbolized TMSL1, TMSL2, etc., respectively. Li et al. (1996) established that in the mouse there is a single Tmsb4 gene and that the lymphoid-specific transcript is generated by extending the ubiquitous exon 1 with an alternate downstream splice site. By interspecific backcross mapping, they located the mouse gene, which they symbolized Ptmb4, to the distal region of the mouse X chromosome, linked to Btk and Gja6. Thus, the human gene could be predicted to reside on the X chromosome in the general region of Xq21.3-q22, where BTK is located. By analysis of somatic cell hybrids, the thymosin-beta-4, or TB4X, gene were mapped to the X chromosome. They noted that a homologous gene, TB4Y, is present on the Y chromosome.

Summary of Invention Paragraph - BSTX (239):

[0237] It was stated that prostate carcinoma is the most prevalent form of cancer in males and the second leading cause of cancer death among older males. The use of the serum prostate-specific antigen test permits early detection of human prostate cancer; however, early detection has not been accompanied by an improvement in determining which tumors may progress to the metastatic stage.

The process of tumor metastasis is a multistage event involving local invasion and destruction of extracellular matrix; intravasation into blood vessels, lymphatics or other channels of transport; survival in the circulation; extravasation out of the vessels into the secondary site; and growth in the new location. Common to many components of the metastatic process is the requirement for tumor cell motility. A well-characterized series of cell lines that showed varying metastatic potential was developed from the Dunning rat prostate carcinoma. A direct correlation between cell motility and metastatic potential in the Dunning cell lines was shown. In studies comparing gene expression in poorly and highly motile metastatic cell lines derived from Dunning rat prostate carcinoma using differential mRNA display, Bao et al. (1996) found a novel member of the thymosin-beta family of actin-binding molecules. The molecule, named thymosin-beta-15 by them, was found to deregulate motility in prostate cells directly. In addition, it was expressed in advanced human prostate cancer specimens, but not in normal human prostate or benign prostatic hyperplasia, suggesting its potential use as a new marker for prostate carcinoma progression. Bao et al. (1996) found that thymosin-beta-15 levels correlated positively with the Gleason tumor grade. Coffey (1996) pointed out that the upregulation of thymosin-beta-15 as a positive motility factor and the down regulation of the motility suppressor KAI1 (OMIM-600623) provide the 'yin and yang' for metastasis; he speculated that these pathways may provide a new target for therapy.

Summary of Invention Paragraph - BSTX (243):

[0241] The nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to prostate cancer, immunological and autoimmune disorders (i.e., hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen, thymus, lung, and peritoneal macrophages and/or other pathologies and disorders. For example, a cDNA encoding the Beta Thymosin-like protein may be useful in gene therapy, and the Beta Thymosin-like protein may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer including but not limited to prostate cancer, immunological and autoimmune disorders (i.e., hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen, thymus, lung, and peritoneal macrophages. The novel nucleic acid encoding Beta Thymosin-like protein, and the Beta Thymosin-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

Summary of Invention - Table CWU - BSTL (76):

76TABLE 5C BLAST results for MOL5 Gene Index/ Length Identity Positives
 Identifier Protein/Organism (aa) (%) (%) Expect
 ref.vertline.NP_068832.1.vertline. thymosin_beta, 45 37/45 38/45 5e-06
 identified in (82%) (84%) neuroblastoma cells [Homo sapiens]
 pir.vertline..vertline.I52084 thymosin_beta-4 56 27/39 33/39 2e-04 precursor -
 rat (69%) (84%) (fragment) sp.vertline.P20065.vertline.TYB4_MOUSE THYMOSIN
BETA-4 50 27/39 33/39 3e-04 (69%) (84%) gb.vertline.AAA36746.1.vertline.
thymosin_beta-10 49 24/40 32/40 0.002 (M92383) [Homo sapiens] (60%) (80%)
 gb.vertline.AAB37101.1.vertline. thymosin_beta- 45 31/39 34/39 0.002 (U25684)
 like protein (79%) (86%) [Rattus norvegicus]

PGPUB-DOCUMENT-NUMBER: 20040024181

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040024181 A1

TITLE: Novel human proteins, polynucleotides encoding them and
methods of using the same

PUBLICATION-DATE: February 5, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gangolli, Esha A.	Madison	CT	US	
Spytek, Kimberly A.	New Haven	CT	US	
Gilbert, Jennifer	Madison	CT	US	
Casman, Stacie	North Haven	CT	US	
Blalock, Angela	Branford	CT	US	
Li, Li	Branford	CT	US	
Vernet, Corine	Branford	CT	US	
Shenoy, Suresh	Branford	CT	US	
Mishra, Vishnu S.	Gainesville	FL	US	
Furtak, Katarzyna	Ansonia	CT	US	
Gerlach, Valerie L.	Branford	CT	US	
Edinger, Shlomit	New Haven	CT	US	
Malyanker, Uriel	Branford	CT	US	
Stone, David	Guilford	CT	US	
Millet, Isabelle	Milford	CT	US	
Smithson, Glenda	Guilford	CT	US	
Gunther, Erik	Branford	CT	US	
Ellerman, Karen	Branford	CT	US	
Padigar, Muralidhara	Branford	CT	US	
Taupier, Raymond J. JR.	East Haven	CT	US	
Anderson, David W.	Branford	CT	US	

APPL-NO: 10/ 055569

DATE FILED: October 26, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60243642 20001026 US

non-provisional-of-provisional 60243320 20001026 US

non-provisional-of-provisional 60243592 20001026 US

non-provisional-of-provisional 60243681 20001027 US

non-provisional-of-provisional 60243863 20001027 US

non-provisional-of-provisional 60244443 20001031 US

non-provisional-of-provisional 60245029 20001101 US

non-provisional-of-provisional 60244995 20001101 US

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non-provisional-of-provisional 60245316 20001102 US

non-provisional-of-provisional 60262994 20010119 US

non-provisional-of-provisional 60269056 20010215 US

non-provisional-of-provisional 60272923 20010302 US

non-provisional-of-provisional 60276565 20010315 US

non-provisional-of-provisional 60318119 20010907 US

US-CL-CURRENT: 530/350, 435/320.1 , 435/325 , 435/69.1 , 536/23.5

ABSTRACT:

Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

RELATED APPLICATIONS

[0001] This application claims priority to U.S. S. No. 60/243,642, filed Oct. 26, 2000; U.S. S. No. 60/243,320, filed Oct. 26, 2000; U.S. S. No. 60/243,592, filed Oct. 26, 2000; U.S. S. No. 60/243,681, filed Oct. 27, 2000; U.S. S. No. 60/243,863, filed Oct. 27, 2000; U.S. S. No. 60/244,443, filed Oct. 31, 2000; U.S. S. No. 60/245,029, filed Nov. 1, 2000; U.S. S. No. 60/244,995, filed Nov. 1, 2000; U.S. S. No. 60/245,293, filed Nov. 2, 2000; U.S. S. No. 60/245,315, filed Nov. 2, 2000; U.S. S. No. 60/245,316, filed Nov. 2, 2000; U.S. S. No. 60/262,994, filed Jan. 19, 2001; U.S. S. No. 60/269,056, filed Feb. 15, 2001, U.S. S. No. 60/272,923, filed Mar. 2, 2001, U.S. S. No. 60/276,565, filed Mar. 15, 2001, and U.S. S. No. 60/318,119, filed Sep. 17, 2001 each of which is incorporated by reference in its entirety.

----- KWIC -----

Summary of Invention Paragraph - BSTX (14):

[0013] The beta-thymosins comprise a family of structurally related, highly conserved acidic polypeptides, originally isolated from calf thymus. A number of peptides belong to this family. They include, thymosin beta-4 is a small polypeptide that was first isolated as a thymic hormone and induced terminal deoxynucleotidyltransferase, thymosin beta-9 (and beta-8) in bovine and pig, thymosin beta-10 in man and rat, thymosin beta-11 and beta-12 in trout and human Nb thymosin beta. They found in high quantity in thymus and spleen but are also widely distributed in many tissues. They have been shown to bind to actin monomers and thus to inhibit actin polymerization

Summary of Invention Paragraph - BSTX (15):

[0014] Thymosin beta10 is a small conserved acidic protein involved in the inhibition of actin polymerization. Studies have demonstrated that thymosin

beta 10 expression is regulated by extracellular signals that stimulate growth of thyroid cells both in vitro and in vivo, and suggest a role for this protein in thyroid diseases characterized by proliferation of follicular cells (10366416). Other studies have demonstrated that thymosin beta-10 is overexpressed in rat thyroid transformed cell lines and in human thyroid carcinoma tissues and cell lines. This evidence suggests that thymosin beta-10 detection may be considered a potential tool for the diagnosis of several human neoplasias (10487837).

Summary of Invention Paragraph - BSTX (52):

[0049] NOV11 is homologous to members of the Thymosin beta 10-like family of proteins. Thus, the NOV11 nucleic acids, polypeptides, antibodies and related compounds according to the invention will be useful in therapeutic and diagnostic applications implicated in, for example; prostate cancer, immunological and autoimmune disorders (ie hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, pathological disorders involving spleen, thymus, lung, and peritoneal macrophages and/or other pathologies/disorders. The NOVX nucleic acids and polypeptides can also be used to screen for molecules, which inhibit or enhance NOVX activity or function. Specifically, the nucleic acids and polypeptides according to the invention may be used as targets for the identification of small molecules that modulate or inhibit, e.g., neurogenesis, cell differentiation, cell proliferation, hematopoiesis, wound healing and angiogenesis. Additional utilities for the NOVX nucleic acids and polypeptides according to the invention are disclosed herein.

Summary of Invention Paragraph - BSTX (224):

[0221] NOV11 includes in vivo novel Thymosin beta-10-like proteins disclosed below. The disclosed proteins have been named NOV11a and NOV11b.

Summary of Invention Paragraph - BSTX (226):

[0223] A disclosed NOV11a nucleic acid of 129 nucleotides (also referred to GMAC079400_A) encoding a novel Thymosin beta-10-like protein is shown in Table 11A. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 28-30 and ending with a TAA codon at nucleotides 157-159. Putative untranslated regions upstream from the initiation codon and downstream from the termination codon are underlined in Table 11A, and the start and stop codons are in bold letters.

Summary of Invention Paragraph - BSTX (227):

[0224] The disclosed NOV11a nucleic acid sequence has 172 of 190 bases (90%) identical to a Homo sapiens Thymosin beta-10 mRNA (GENBANK-ID: S54005) (E=3.1e.sup.-28).

Summary of Invention Paragraph - BSTX (229):

[0226] The NOV11a amino acid sequence has 37 of 44 amino acid residues (84%) identical to, and 40 of 44 amino acid residues (90%) similar to, the Rattus norvegicus 44 amino acid residue Thymosin beta-10 protein (A27266) (E=2.4e.sup.-12). The global sequence homology is 88.372% amino acid homology and 86.047% amino acid identity.

Summary of Invention Paragraph - BSTX (230):

[0227] NOV11a is predicted to be expressed in the Metastatic Melanoma tissues because of the expression pattern of a closely related Homo sapiens Thymosin beta-10 homolog (GENBANK-ID: S54005).

Summary of Invention Paragraph - BSTX (232):

[0229] A disclosed NOV11b nucleic acid of 173 nucleotides (also referred to CG109754-01) encoding a novel Thymosin beta-10-like protein is shown in Table

11C. An open reading frame was identified beginning with an ATG initiation codon at nucleotides 27-29 and ending with a TAA codon at nucleotides 156-158. Putative untranslated regions upstream from the initiation codon and downstream from the termination codon are underlined in Table 11C, and the start and stop codons are in bold letters.

Summary of Invention Paragraph - BSTX (233):

[0230] The disclosed NOV11b nucleic acid sequence, localized to chromosome 2, has 155 of 168 bases (92%) identical to a Homo sapiens Thymosin beta-10 mRNA (gb:GENBANK-.ID:HUMTHMBX.vertline.acc:M92381.1) (E=4.1.sup.-25).

Summary of Invention Paragraph - BSTX (234):

[0231] A disclosed NOV11b polypeptide (SEQ ID NO:34) encoded by SEQ ID NO:33 is 43 amino acid residues and is presented using the one-letter amino acid code in Table 11D. Signal P, Psort and/or Hydropathy results predict that NOV11b does not contain a signal peptide and is likely to be localized to the nucleus with a certainty of 0.5426. Although PSORT suggests the NOV11b polypeptide may be localized in the nucleus, the NOV11b protein is similar to the Thymosin family, some members of which are released extracellularly. Therefore it is likely that this novel Thymosin Beta 10-like protein is localized to the extracellular space.

Summary of Invention Paragraph - BSTX (235):

[0232] The NOV11b amino acid sequence has 36 of 43 amino acid residues (83%) identical to, and 39 of 43 amino acid residues (90%) similar to, the Homo sapiens 43 amino acid residue Thymosin beta-10 protein (ptnr:SWISSNEW-ACC:P13472) (E=1.7e.sup.-2). NOV11b protein is 43 amino acids long, which is the same length as public protein P13472. NOV11b protein differs at eight amino acid positions. NOV11b begins with a methionine that the public GenBank submission is lacking. In addition to this, there are six single amino acid changes (M6V, E8G, D14N, K15R, 134T, E35G) and a single amino acid deletion (E37-). This number of changes in such a short peptide indicates that NOV11b protein is derived from a different gene than the public protein.

Summary of Invention Paragraph - BSTX (236):

[0233] NOV11b is predicted to be expressed in brain and neuroblastoma tissues because of the expression pattern of a closely related Homo sapiens Thymosin beta-10 homolog (GENBANK-ID: gb:GENBANK-ID:HUMTHMBX.vertline.acc:M92381.1).

Summary of Invention Paragraph - BSTX (242):

[0239] The protein similarity information, expression pattern, and map location for the NOV11 protein and nucleic acid suggest that NOV11 may have important structural and/or physiological functions characteristic of the Thymosin beta 10 family. Therefore, the NOV11 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in various diseases and disorders described below and/or other pathologies. For example, the NOV11 compositions of the present invention will have efficacy for treatment of patients suffering from prostate cancer, immunological and autoimmune disorders (ie hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, pathological disorders involving spleen, thymus, lung, and peritoneal macrophages and/or other pathologies and disorders. The NOV11 nucleic acid encoding Thymosin beta 10-like protein, and the Thymosin beta 10-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed.

Summary of Invention - Table CWU - BSTL (1):

1TABLE A Sequences and Corresponding SEQ ID Numbers SEQ ID NO NOVX
(nucleic SEQ ID NO Assignment Internal Identification acid) (polypeptide)
Homology 1 3352274 1 2 Calpain-like 2 21421174 3 4 Epsin-like 3
AC025263_da1 5 6 Low Density Lipoprotein B-like 4 AC026756_da1 7 8
Purinoreceptor 5a sggc_draft_dj895c5_ 9 10 CG8841-like 20000811_da1 5b
CG54443-02 11 12 CG8841-like 6a SC134912642_da1 13 14 Synaptotagmin-like 6b
CG56106-01 15 16 Synaptotagmin-like 7 wugc_draft_h_nh0781m 17 18 Serine
Protease TLSP-like 21_20000809_da1 8a 134913441_EXT 19 20 Glypican-2
Precursor-like 8b CG50970-02 21 22 Glypican-2 Precursor-like 8c CG50970-03
23 24 Glypican-2 Precursor-like 8d CG50970-04 25 26 Glypican-2 Precursor-like
9 AC011005_da2/1399435 27 28 Mitogen-activated protein kinase 78 kinase
2-like 10 sggc_draft_c333e1_ 29 30 Zinc Finger Protein 276 C2H2-type
20000804_da2 11a GMAC079400_A 31 32 Thymosin beta 10-like 11b CG109754-01 33
34 Thymosin beta 10-like

Summary of Invention - Table CWU - BSTL (69):

69TABLE 11F BLAST results for NOV11a Gene Index/ Length Identity
Identifier Protein/Organism (aa) (%) Positives (%) Expect
gi.vertline.339697.vertline.gb.vertli- ne.AAA36746.1.vertline. thymosin
beta-10 49 37/44 40/44 4e-04 (M92383) [Homo sapiens] (84%) (90%)
gi.vertline.10863895.vertline- .ref.vertline.NP_ thymosin, beta 10 42 34/42
39/42 0.002 066926.1.vertline. [Homo sapiens] (80%) (91%)
gi.vertline.223789.vertline.prf.vertline. .vertline.0912169A thymosin 44 37/44
40/44 0.005 beta10,Arg (84%) (90%) [Oryctolagus cuniculus]
gi.vertline.2143995.vertline.pir.vertline. .vertline.I52084 thymosin beta-4 43
36/43 39/43 0.019 precursor (83%) (89%) (fragment) [Rattus norvegicus]

Summary of Invention - Table CWU - BSTL (70):

70TABLE 11H BLASTX results for NOV11 Smallest Sum Reading High Prob
Sequences producing High-scoring Segment Pairs: Frame Score P(N) N ptkm1
patp:AAAY80267 Thymosin beta 4 peptide isoform Tbeta10, Unknown 43 aa.. +1 169
7.2e-12 1

Detail Description Paragraph - DETX (192):

[0684] NOV11: Thymosin beta 10-Like

Detail Description Paragraph - DETX (198):

[0690] Panel 1.3D Summary Ag2431 The NON11 gene, a homolog of thymosin beta
10, is most highly expressed in the hippocampus (CT=24.2) and is expressed
widely in the CNS. This gene appears to be important in the process of
gliosis, which is a hallmark of all of the neurodegenerative diseases.
Furthermore, the formation of a glial scar is one of the principle barriers to
neuroregeneration in response to spinal cord injury and head trauma.
Therefore, the selective down-regulation of this gene and/or its protein
product may be beneficial in the treatment of spine or head injury, or in any
of the neurodegenerative diseases (Alzheimer's, Parkinson's, Huntington's,
spinocerebellar ataxia, etc).

Detail Description Paragraph - DETX (202):

[0694] Panel 4L) Summary Ag2431 The NOV11 gene is ubiquitously expressed
throughout this panel in both normal cell types and cell lines, regardless of
their activation status. This gene encodes a protein that has homology with
Thymosin beta-10. Some reports indicate that thymosin beta 10 (as thymosin
beta 4- which is functionally very similar) is an effective regulator of a
large subset of actin filaments in living cells. Reduced expression of
thymosin beta-10 may contribute to the senescent phenotype by reducing EC
plasticity and thus impairing their response to migratory stimuli. Therefore,
therapeutics designed with the protein encoded for by the NOV11 gene may play a
role in maintaining or restoring normal function of lymphoid, lung, dermal

fibroblasts, endothelial cells and could be beneficial in preventing aging of the cells.

Detail Description Paragraph - DETX (203):

[0695] Panel CNS_neurodegenerataion_v1.0 Summary Ag2431 Expression of the NOV11 gene is restricted to a few samples in this panel, with highest expression in the cerebral cortex of an Alzheimer's patient (CT=33.5). While no association between the expression of this gene and the presence of Alzheimer's disease is detected in this panel, these results confirm the expression of this gene in the brains of a further set of individuals. Please see Panel 1.3D for a discussion of potential utility of this gene in the central nervous system (Carpintero et al., Expression of the thymosin beta 10 gene in normal and kainic acid-treated rat forebrain. Brain Res Mol Brain Res. 70:141-6, 1999).

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ABSTRACT:

The present invention describes novel methods that measure in a mammal the level of at least one biomarker, such as a protein and/or mRNA transcript. Based on the level of at least one biomarker in a mammal exposed to a test compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to a test compound, the ability of the test compound to inhibit tyrosine kinase activity can be determined. The invention also relates to novel methods, wherein a change in the level of at least one biomarker in a mammal exposed to a compound, compared to the level of the biomarker(s) in a mammal that has not been exposed to the compound, indicates whether the mammal is being exposed to, or is experiencing or will experience a therapeutic or toxic effect in response to, a compound that inhibit tyrosine kinase activity.

[0001] This application claims benefit of priority from U.S. provisional application Ser. Nos 60/380,872, filed May 17, 2002, 60/448,922, filed Feb. 24, 2003, and 60/448,874, filed Feb. 24, 2003, all of which are incorporated by reference in their entirety.

----- KWIC -----

Brief Description of Drawings Paragraph - DRTX

(13):

[0016] FIG. 12 shows mRNA and protein sequences for eucaryotic initiation factor 4A11 (SEQ ID NOS 75-76, respectively), human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792) (SEQ ID NOS 77-78, respectively), Homo sapiens thymosin beta-10 (SEQ ID NOS 79-80, respectively), Homo sapiens hnRNPcore protein A1 (SEQ ID NOS 81-82, respectively), human leucocyte antigen (CD37) (SEQ ID NOS 83-84, respectively), human MHC class II HLA-DR beta-1 (SEQ ID NOS 85-86, respectively), Homo sapiens translation initiation factor eIF3 p66 subunit (SEQ ID NOS 87-88, respectively), Homo sapiens nm23-H2 gene (SEQ ID NOS 89-90, respectively), human acidic ribosomal phosphoprotein P0 (SEQ ID NOS 91-92, respectively), human cyclophilin (SEQ ID NOS 93-94, respectively), Genbank Accession No. A1541256 (cDNA) (SEQ ID NO: 95), human T-cell receptor active beta chain (SEQ ID NOS 96-97, respectively), human MHC class II lymphocyte antigen (HLA-DP) beta chain (SEQ ID NOS 98-99, respectively), human KIAA0195 (SEQ ID NOS 100-101, respectively), Homo sapiens MAP kinase kinase 3 (MKK3) (SEQ ID NOS 102-103, respectively), human beta-tubulin class III isotype (beta-3) (SEQ ID NOS 104-105, respectively), human tropomyosin (SEQ ID NOS 106-107, respectively), 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C (SEQ ID NOS 108-109, respectively), human MLC emb gene for embryonic myosin alkaline light chain (SEQ ID NOS 110-111, respectively), Homo sapiens glyoxalase II (SEQ ID NOS 112-113, respectively), Homo sapiens trans-golgi network glycoprotein 48 (SEQ ID NOS 114-115, respectively), histone H2B (SEQ ID NOS 116-117, respectively), human RLIP76 protein (SEQ ID NOS 118-119, respectively), Genbank Accession No. W26677 (human retina cDNA) (SEQ ID NO: 120), human PMI gene for a putative receptor protein (SEQ ID NOS 121-122, respectively), human DNA-binding protein A (dbpA) (SEQ ID NOS 123-124, respectively), human ITIH4 (SEQ ID NOS 125-126, respectively), IL-8 (SEQ ID NOS 182-183, respectively) and C-reactive protein (SEQ ID NOS 184-185, respectively).

Detail Description Paragraph - DETX (37):

[0068] (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A 11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human

DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (43):

[0074] (b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

Detail Description Paragraph - DETX (46):

[0077] (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4,

soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (52):

[0083] (b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

Detail Description Paragraph - DETX (55):

[0086] (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine

phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (61):

[0092] (b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

Detail Description Paragraph - DETX (64):

[0095] (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66

subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (70):

[0101] (b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1,

Detail Description Paragraph - DETX (74):

[0105] (a) measuring in the mammal the level of at least one of the

following proteins and/or mRNA transcripts for such proteins and/or genes:
 PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC,
 eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled
 receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10
gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human
 MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66
 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0,
 human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human
 T-cell receptor active beta chain, human MHC class II lymphocyte antigen
 (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76
 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription
 factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine
 phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA
 polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B
 member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase
 p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1,
 GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha.,
 TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4,
 soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III
 isotype (beta-3), human tropomyosin, 1-phosphatidyl
 inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic
 myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens
 trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677
 (human retina cDNA), human PMI gene for a putative receptor protein, human
 DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A,
 von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2,
 phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase
 p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44,
 ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (79):

[0110] (a) measuring in a mammal with cancer the level of at least one of
 the following proteins and/or mRNA transcripts for such proteins and/or genes:
 PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC,
 eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled
 receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10
gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human
 MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66
 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0,
 human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human
 T-cell receptor active beta chain, human MHC class II lymphocyte antigen
 (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76
 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription
 factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine
 phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA
 polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B
 member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase
 p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1,
 GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha.,
 TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4,
 soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III
 isotype (beta-3), human tropomyosin, 1-phosphatidyl
 inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic
 myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens
 trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677
 (human retina cDNA), human PMI gene for a putative receptor protein, human
 DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A,
 von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2,
 phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase

p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (88):

[0119] Other embodiments also include any of the proceeding methods, wherein the "difference" refers to an increase in the level of at least one of the following protein(s) and/or mRNA transcript(s): PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2B, human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ephrin receptor EphB4, OB-cadherin 1, phosphoinositol 3-kinase p85 subunit, mucin 1 and gelsolin, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (94):

[0125] Other embodiments also include any of the proceeding methods wherein the mammal has thyroid cancer, and wherein the "difference" refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), histone H2b and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (95):

[0126] Other embodiments also include any of the proceeding methods wherein the mammal has pancreatic cancer, and wherein the "difference" refers to an increase in the level of at least one of eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (97):

[0128] Other embodiments also include any of the proceeding methods wherein the mammal has prostate cancer, and wherein the "difference" refers to an increase in the level of at least one of VEGF, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor, Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, and human MHC class II lymphocyte antigen (HLA-DP) beta chain protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (98):

[0129] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the "difference" refers to an increase in the level of at least one of Homo sapiens thymosin beta-10 gene, Homo sapiens MAP kinase kinase 3 (MKK3) and histone H2B member R protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (100):

[0131] Other embodiments also include any of the proceeding methods, wherein the "difference" refers to a decrease in the level of at least one of the following protein(s) and/or mRNA transcript(s): ITIH4, PAI-1, soluble VEGF receptor 2 (sVEGFR2), Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human KIAA0195, human beta-tubulin class III isotype (beta-3), Homo sapiens MAP kinase kinase 3 (MKK3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78, MPIF-1, MMP7, MIG, cdc2 related protein kinase, and phosphoinositol 3-kinase p110 subunit, as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (103):

[0134] Other embodiments also include any of the proceeding methods wherein the mammal has parotid cancer, and wherein the "difference" refers to a decrease in the level of at least one of Homo sapiens thymosin beta-10 gene, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, human MHC class II lymphocyte antigen (HLA-DP), human beta-tubulin class III isotype (beta-3), and human RLIP76 protein(s) and/or mRNA transcript(s) as measured after exposure to a compound that inhibits tyrosine kinase activity, compared to the level of the same protein(s) and/or mRNA transcript(s) as measured before exposure to the compound.

Detail Description Paragraph - DETX (109):

[0140] (a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and

Detail Description Paragraph - DETX (112):

[0143] (i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin

receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1;

Detail Description Paragraph - DETX (367):

[0395] Samples of whole blood from human patients were taken before and 27 days after the first dose of Compound A (in other words, samples were taken on day 0 and day 28; patients were dosed about 2 times per day on day 1-day 27, and following the first dose on day 28, the sample of blood was taken to measure biomarker(s). An Affymetrix GeneChip analysis of the RNA transcripts present in patient plasma before and after exposure to Compound A indicated that the levels of 26 transcripts were increased and/or decreased after exposure to Compound A (see FIG. 5). Thus, 26 proteins/transcripts were identified as biomarkers for a compound that inhibits tyrosine kinase, such as Compound A: eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06792), Homo sapiens thymosin beta-10, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, Genbank Accession No. A1541256 (cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, human KIAA0195, Homo sapiens MAP kinase kinase 3 (MKK3), human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C, human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B member R, human RLIP76 protein, Genbank Accession No. W26677 (human retina cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA). See FIG. 12 for sequences for these biomarkers.

Claims Text - CLTX (2):

1. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising: (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative

receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (b), exposing the mammal to the test compound; and (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a), wherein a difference in the level of said protein and/or mRNA transcript measured in (c), compared to the level of protein and/or mRNA transcript measured in step (a) indicates that the test compound is an inhibitor of tyrosine kinase in the mammal.

Claims Text - CLTX (3):

2. A method for determining whether a test compound inhibits tyrosine kinase activity in a mammal, comprising: (a) exposing the mammal to the test compound; and (b) following the exposing of step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1, wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the compound is an inhibitor of tyrosine kinase in the mammal.

Claims Text - CLTX (4):

3. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising: (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore

protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (b), exposing the mammal to the test compound; and (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a), wherein a difference in the level of said protein and/or mRNA measured in (c), compared to the level of protein and/or mRNA in step (a) indicates that the mammal has been exposed to a test compound that inhibits tyrosine kinase activity.

Claims Text - CLTX (5):

4. A method for determining whether a mammal has been exposed to a test compound that inhibits tyrosine kinase activity, comprising (a) exposing the mammal to the test compound; and (b) following the exposing of step (a), measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1, wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said test compound, indicates that the mammal has been exposed to a test compound that is an inhibitor of tyrosine kinase.

Claims Text - CLTX (6):

5. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising: (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. AI541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (b), exposing the mammal to the compound; and (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a), wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that that the mammal is responding to the compound that inhibits tyrosine kinase activity.

Claims Text - CLTX (7):

6. A method for determining whether a mammal is responding to a compound that inhibits tyrosine kinase activity, comprising: (a) exposing the mammal to the compound; and (b) following the exposing step (a), measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human

(clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1, wherein a difference in the level of said protein and/or mRNA measured in (b), compared to the level of protein and/or mRNA in a mammal that has not been exposed to said compound, indicates that the mammal is responding to the compound that inhibits tyrosine kinase.

Claims Text - CLTX (8):

7. A method for identifying a mammal that will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for identifying the mammal comprises: (a) measuring in the mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677

(Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (b) exposing the mammal to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase; and (c) following the exposing of step (b), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts measured in step (a), wherein a difference in the level of said protein and/or mRNA transcripts measured in (c), compared to the level of protein and/or mRNA transcript for said protein in step (a) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

Claims Text - CLTX (9):

8. A method for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer comprising administering at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase, wherein the method for testing or predicting comprises: (a) measuring in a mammal with cancer the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (b) measuring in the same type of mammal without cancer, the level of at least one of the same proteins and/or mRNA transcripts measured in step (a); (c) comparing levels of said proteins and/or mRNA transcripts measured in (a) and (b); wherein a difference in the level of said protein and/or mRNA in the mammal with cancer as measured in step (a), compared to the level of said protein and/or mRNA in the mammal without cancer as measured in step (b), indicates that the mammal will respond therapeutically to at least one inhibitor of a VEGFR and/or PDGFR tyrosine kinase.

Claims Text - CLTX (23):

22. A kit comprising: (a) antibody and/or nucleic acid for detecting the presence of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; and (b) instructions for determining whether or not a mammal will respond therapeutically to a method of treating cancer comprising administering a compound that inhibits tyrosine kinase activity.

Claims Text - CLTX (24):

23. A kit of claim 22, wherein said instructions comprise the steps of: (i) measuring in a mammal the level of at least one of the following proteins and/or mRNA transcripts for such proteins and/or genes: PAI-1, TIMP-1, vinculin, VEGF, PLGF, VEGF/PLGF heterodimers, MIG, IP-10, I-TAC, eucaryotic initiation factor 4A11, human (clone 5) orphan G protein-coupled receptor (Genbank Accession No. L06797; CXCR4), Homo sapiens thymosin beta-10 gene, Homo sapiens hnRNPcore protein A1, human leucocyte antigen (CD37), human MHC class II HLA-DR beta-1, Homo sapiens translation initiation factor eIF3 p66 subunit, Homo sapiens nm23-H2 gene, human acidic ribosomal phosphoprotein P0, human cyclophilin, GenBank Accession No. A1541256 (Homo sapiens cDNA), human T-cell receptor active beta chain, human MHC class II lymphocyte antigen (HLA-DP) beta chain, Homo sapiens MAP kinase kinase 3 (MKK3), human RLIP76 protein, MMP-9, lactoferrin, lipocalin-2, CD24 antigen, basic transcription factor 3 homologue, c-jun proto-oncogene, c-fos cellular oncogene, tyrosine phosphatase non-receptor type 2, cdc2 related protein kinase, cyclin C, DNA polymerase gamma, protein kinase C alpha, lipocortin II/annexin A2, histone H2B member R, amphiregulin, basic transcription factor 3, phosphoinositol 3-kinase p110 subunit, GCP-2, IL-1.alpha., IL-1.beta., IL-2, NT4, GCP-2, IGFBP-1, GRO-.beta., TNFR1, FLT3L, IL-6, IL-8, C-reactive protein, MCP-1, TNF.alpha., TARC, MMP7, leptin, pro-MMP1 (interstitial collagenase precursor), ITIH4, soluble VEGF receptor 2 (sVEGFR2), human KIAA0195, human beta-tubulin class III isotype (beta-3), human tropomyosin, 1-phosphatidyl inositol-4-phosphate-5-kinase isoform C; human MLC emb gene for embryonic myosin alkaline light chain, Homo sapiens glyoxalase II, Homo sapiens

trans-golgi network glycoprotein 48, histone H2B, Genbank Accession No. W26677 (Homo sapiens cDNA), human PMI gene for a putative receptor protein, human DNA-binding protein A (dbpA), ephrin receptor EphB4, hanukah factor/granzyme A, von Hippel-Lindau (VHL) tumor suppressor, OB-cadherin 1, OB-cadherin 2, phosphoinositol 3-phosphate-binding protein-3 (PEPP3), phosphoinositol 3-kinase p85 subunit, mucin 1, hepatitis C-associated microtubular aggregate p44, ErbB3/HER3 receptor tyrosine kinase, gelsolin, cyclin D2, ENA-78 and MPIF-1; (ii) exposing the mammal to a compound that inhibits tyrosine kinase activity; and (iii) following the exposing step of (ii), measuring in the mammal the level of at least one of the proteins and/or mRNA transcripts for such proteins measured in step (i); wherein a difference in the level of said proteins and/or mRNA transcripts measured in (iii), compared to the level of proteins and or mRNA transcripts measured in step (i) indicates that the mammal will respond therapeutically to a method of treating cancer comprising administering the compound that inhibits tyrosine kinase activity.

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non-provisional-of-provisional 60278199 20010323 US
non-provisional-of-provisional 60279274 20010328 US
non-provisional-of-provisional 60280238 20010330 US
non-provisional-of-provisional 60280899 20010402 US
non-provisional-of-provisional 60310797 20010808 US
non-provisional-of-provisional 60312284 20010814 US
non-provisional-of-provisional 60322294 20010914 US
non-provisional-of-provisional 60322295 20010914 US
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ABSTRACT:

Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

RELATED APPLICATIONS

[0001] This is a request for filing a new nonprovisional application under 37 C.F.R. .sctn.1.53(b). This application claims priority to U.S. S. No. 60/268,221 filed on Feb. 12, 2001 (Cura 569); U.S. S. No. 60/335,109 filed on Oct. 31, 2001 (Cura 569 F1); U.S. S. No. 60/312,284 filed on Aug. 14, 2001 (Cura 569 IFC-01); U.S. S. No. 60/268,496 filed on Feb. 13, 2001 (Cura 270); U.S. S. No. 60/276,703 filed on Mar. 16, 2001 (Cura 570 B1); U.S. S. No. 60/330,293 filed on Oct. 18, 2001 (Cura 570 C1); U.S. S. No. 60/322,127 filed on Nov. 21, 2001 (Cura 570 F IFC-02); U.S. S. No. 60/280,899 filed on Apr. 2, 2001 (Cura 570 G1); U.S. S. No. 60/310,797 filed on Aug. 8, 2001 (Cura 570

IFC-01); U.S. S. No. 60/268,646 filed on Feb. 14, 2001 (Cura 571); U.S. S. No. 60/276,399 filed on Mar. 16, 2001 (Cura 571 A); U.S. S. No. 60/268,665 filed on Feb. 14, 2001 (Cura 572); U.S. S. No. 60/269,530 filed on Feb. 16, 2001 (Cura 572 A); U.S. S. No. 60/269,136 filed on Feb. 15, 2001 (Cura 573); U.S. S. No. 60/279,274 filed on Mar. 28, 2001 (Cura 573 AI); U.S. S. No. 60/331,772 filed on Nov. 21, 2001 (Cura 573 D IFC-01); U.S. S. No. 60/322,295 filed on Sep. 14, 2001 (Cura 573 I1); U.S. S. No. 60/278,199 filed on Mar. 23, 2001 (Cura 573 J1); U.S. S. No. 60/276,405 filed on Mar. 15, 2001 (Cura 573 J11); U.S. S. No. 60/269,310 filed on Feb. 16, 2001 (Cura 574); U.S. S. No. 60/280,238 filed on Mar. 30, 2001 (Cura 574 A1); U.S. S. No. 60/322,294 filed on Sep. 14, 2001 (Cura 574 B1); U.S. S. No. 60/335,104 filed on Oct. 31, 2001 (Cura 574 D1); each of which is incorporated by reference in its entirety.

----- KWIC -----

Summary of Invention Paragraph - BSTX (4):

[0003] The present invention is based in part on nucleic acids encoding proteins that are new members of the following protein families: Zinc Finger-like proteins, Pepsin A Precursor-like proteins, Ribonuclease Pancreatic-like proteins, Ser/Thr Protein Kinase-like proteins, Glycodelin-like proteins, Neuropathy Target Esterase/Swiss Cheese Protein-like proteins, Acid-Sensitive Potassium Channel Protein Task-like protein, Novel Ribosomal Protein L8-like proteins, Prostaglandin Omega Hydroxylase-like proteins, Myeloid Upregulated Protein-like proteins, Testicular Serine Protease-like proteins, Hepatitis B Virus (HBV) Associated Factor-like proteins, Apolipoprotein L-like proteins, Rh Type C Glycoprotein-like proteins, Copine III-like proteins, Carboxypeptidase B Pancreatic-like proteins, Ribosomal Protein L29-like proteins, Ser/Thr kinase-like proteins, Metallaproteinase-Disintegrin (ADAM30)-like proteins, Bone Morphogenetic Protein 11-like proteins, Protein Tyrosine Phosphatase-like proteins, Aldo-Keto Reductase Family 7, Member A3-like proteins, Ral Guanine Nucleotide Exchange Factor 3-like proteins, Endolyn-like proteins, Arylacetamide Deacetylase-like proteins, GPCR-like proteins, PB39-like proteins, Oxytocin-like proteins, Thymosin beta-4-like proteins, beta Thymosin-like proteins, Thymosin Beta-4-like proteins, Myelin P2-like proteins, Testis Lipid-Binding Protein-like proteins, Intracellular Thrombospondin Domain Containing Protein-like protein, Ornithine Decarboxylase-like protein, Short-Chain Dehydrogenase/Reductase-like protein, Protocadherin Beta 3-like protein and Adrenomedullin Receptor-like protein. More particularly, the invention relates to nucleic acids encoding novel polypeptides, as well as vectors, host cells, antibodies, and recombinant methods for producing these nucleic acids and polypeptides.

Detail Description Paragraph - DETX (565):

[0590] One NOVX protein of the invention, referred to herein as NOV30, includes three Thymosin Beta-4-like proteins. The disclosed proteins have been named NOV30a, NOV30b and NOV30c.

Detail Description Paragraph - DETX (567):

[0592] A disclosed NOV30a (designated CuraGen Acc. No. CG57330-01), which encodes a novel Thymosin Beta-4-like protein and includes the 201 nucleotide sequence (SEQ ID NO:87) is shown in Table 30A. An open reading frame for the mature protein was identified beginning with an ATG initiation codon at nucleotides 49-51 and ending with a TAA stop codon at nucleotides 199-201. Putative untranslated regions are underlined in Table 30A, and the start and stop codons are in bold letters.

Detail Description Paragraph - DETX (568):

[0593] The disclosed NOV30a nucleic acid sequence maps to chromosome Xq21.3-22 and has 161 of 192 bases (83%) identical to a gb:GENBANK-ID:HUMTHYB41acc:MI7733.1 mRNA from Homo sapiens (Human thymosin beta-4 mRNA, complete cds) (E=1.9e.sup.-23).

Detail Description Paragraph - DETX (570):

[0595] The NOV30a amino acid sequence was found to have 31 of 36 amino acid residues (86%) identical to, and 31 of 36 amino acid residues (86%) similar to, the 50 amino acid residue ptnr:SWISSPROT-ACC:P20065 protein from Mus musculus (Mouse) (THYMOSIN BETA-4) (E=1.96e.sup.-10).

Detail Description Paragraph - DETX (575):

[0600] The disclosed NOV30b nucleic acid sequence maps to chromosome 8 and has 216 of 249 bases (86%) identical to a gb:GENBANK-ID:HUMTHYB41acc:MI77- 33.1 mRNA from Homo sapiens (Human thymosin beta-4 mRNA, complete cds) (E=1.1e.sup.-34).

Detail Description Paragraph - DETX (578):

[0603] Expression information was derived from the tissue sources of the sequences that were included in the derivation of the sequence of NOV30b. The sequence is predicted to be expressed in the following tissues because of the expression pattern of (GENBANK-ID: gb:GENBANK-ID:HUMTHYB41- acc:M 17733.1), a closely related Human thymosin beta-4 mRNA, complete cds homolog in species Homo sapiens: Lung, small cell carcinoma.

Detail Description Paragraph - DETX (580):

[0605] A disclosed NOV30c (designated CuraGen Acc. No. CG57330-02), which encodes a novel Thymosin Beta-4-like protein and includes the 201 nucleotide sequence (SEQ ID NO:91) is shown in Table 30F. An open reading frame for the mature protein was identified beginning with an ATG initiation codon at nucleotides 31-33 and ending with a TAA stop codon at nucleotides 199-201. Putative untranslated regions are underlined in Table 30A, and the start and stop codons are in bold letters.

Detail Description Paragraph - DETX (581):

[0606] The disclosed NOV30c nucleic acid sequence maps to chromosome X and has 162 of 192 bases (84%) identical to a gb:GENBANK-ID:HUMTHYB41acc:M177- 33.1 mRNA from Homo sapiens (Human thymosin beta-4 mRNA, complete cds) (E=7.5e.sup.-24).

Detail Description Paragraph - DETX (593):

[0618] Thymosin beta-4 is a small polypeptide whose exact physiological role is not yet known. It was first isolated as a thymic hormone that induces terminal deoxynucleotidyl-transferase. It is found in high quantity in thymus and spleen but is widely distributed in many tissues. It has also been shown to bind to actin monomers and thus to inhibit actin polymerization. See Interpro IPR001152:

Detail Description Paragraph - DETX (594):

[0619] A number of peptides closely related to thymosin beta-4 belong to this family. They include, thymosin beta-9 (and beta-8) in bovine and pig, thymosin beta-10 in man and rat, thymosin beta-11 and beta-12 in trout and human Nb thymosin beta. Thymosin was originally isolated from a partially purified extract of calf thymus, thymosin fraction 5, which induced differentiation of T cells and was partially effective in some immunocompromised animals. Further studies demonstrated that the molecule is ubiquitous; it had been found in all tissues and cell lines analyzed. It is found in highest concentrations in spleen, thymus, lung, and peritoneal

macrophages. Thymosin-beta-4 (T-beta-4) is an actin monomer sequestering protein that may have a critical role in modulating the dynamics of actin polymerization and depolymerization in nonmuscle cells. Its regulatory role is consistent with the many examples of transcriptional regulation of T-beta-4 and of tissue-specific expression. Lymphocytes have a unique T-beta-4 transcript relative to the ubiquitous transcript found in many other tissues and cells. Rat thymosin-beta-4 is synthesized as a 44-amino acid propeptide which is processed into a 43-amino acid peptide by removal of the first methionyl residue. The molecule does not have a signal peptide. Human thymosin-beta-4 has a high degree of homology to rat thymosin-beta-4; the coding regions differ by only 9 nucleotides, and these are all silent base changes.

Detail Description Paragraph - DETX (595):

[0620] A cDNA encoding thymosin-beta-4 has been isolated by differential screening of a cDNA library prepared from leukocytes of an acute lymphocytic leukemia patient. Using Northern blot analysis, the expression of the thymosin-beta-4 mRNA in various primary myeloid and lymphoid malignant cell lines and in hemopoietic cell lines was studied. The pattern of thymosin-beta-4 gene expression suggests that it may be involved in an early phase of the host defense mechanism. A cDNA clone for the human interferon-inducible gene 6-26 has been isolated and shown to be identical to that for the human thymosin-beta-4 gene. By use of a panel of human rodent somatic cell hybrids, it has been shown that the cDNA recognized 7 genes, members of a multigene family, present on chromosomes 1, 2, 4, 9, 11, 20, and X. These genes are symbolized TMSL1, TMSL2, etc., respectively.

Detail Description Paragraph - DETX (596):

[0621] In the mouse there is a single Tmsb4 gene and the lymphoid-specific transcript is generated by extending the ubiquitous exon 1 with an alternate downstream splice site. By interspecific backcross mapping, the mouse gene (designated Ptmb4) has been located to the distal region of the mouse X chromosome, linked to Btk and Gja6. Thus, the human gene could be predicted to reside on the X chromosome in the general region of Xq21.3-q22, where BTK is located. By analysis of somatic cell hybrids, the thymosin-beta-4, or TB4X, gene was mapped to the X chromosome. A homologous gene, TB4Y, is present on the Y chromosome. The TB4X gene escapes X inactivation, and it has been suggested that it should be investigated as a candidate gene for Turner syndrome. Thymosin-beta-4 induces the expression of terminal deoxynucleotidyl transferase activity in vivo and in vitro, inhibits the migration of macrophages, and stimulates the secretion of hypothalamic luteinizing hormone-releasing hormone. It has also been suggested that thymosin beta-4 is required for the metastasis of melanoma cells.

Detail Description Paragraph - DETX (597):

[0622] The protein similarity information, expression pattern, cellular localization, and map location for the NOV30 protein and nucleic acid disclosed herein suggest that this thymosin beta-4-like protein may have important structural and/or physiological functions characteristic of the thymosin beta-4 family. Therefore, the nucleic acids and proteins of the invention are useful in potential diagnostic and therapeutic applications and as a research tool. These include serving as a specific or selective nucleic acid or protein diagnostic and/or prognostic marker, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These also include potential therapeutic applications such as the following: (i) a protein therapeutic, (ii) a small molecule drug target, (iii) an antibody target (therapeutic, diagnostic, drug targeting/cytotoxic antibody), (iv) a nucleic acid useful in gene therapy (gene delivery/gene ablation), (v) an agent promoting tissue regeneration in vitro and in vivo, and (vi) a biological defense weapon.

Detail Description Table CWU - DETL (1):

1TABLE 1 Sequences and Corresponding SEQ ID Numbers Nucleic Amino Acid
 Acid NOVX SEQ ID SEQ ID No. Internal Acc. No. Homology NO. NO. 1 CG56920-01
 Zinc Finger Protein-like Proteins 1 2 2 CG57107-01 Pepsin A Precursor-like
 Protein 3, 5, 7, 4, 6, 8, 9, 11 10, 12 3 CG56936-01 Ribonuclease
 Pancreatic-like 13 14 Proteins 4 CG51707-02 Ser/Thr Protein Kinase-like 15
 16 Proteins 5 CG57081-01 Ser/Thr Protein Kinase-like 17 18 Proteins 6
 CG56684-02 Glycodelin-like Proteins 19 20 7 CG56977-01 Neuropathy Target
 Esterase/Swiss 21 22 Cheese Protein-like Proteins 8 CG57119-01 Acid-Sensitive
 potassium Channel 23 24 Protein Task-like Proteins 9 CG57143-01 Novel
 Ribosomal Protein L8-like 25 26 Proteins 10 CG56860-01 Prostaglandin Omega
 Hydroxylase- 27 28 like Proteins 11 CG57024-01 Myeloid Upregulated
 Protein-like 29 30 Proteins 12 CG57083-01 Testicular Serine Protease-like 31
 32 Proteins .sup. 13a CG56961-01 Hepatitis B Virus (HBV) 33 34 Associated
 Factor-like Proteins 13b CG56961-02 Hepatitis B Virus (HBV) 35 36 Associated
 Factor-like Proteins 14 CG57104-01 Apolipoprotein L-like Proteins 37 38 14b
 CG57104-02 Apolipoprotein L-like Proteins 39 40 15 CG57146-01 Rh Type C
 Glycoprotein-like 41 42 Protein 16 CG57169-01 Copine III-like Protein 43 44
 17 CG57177-01 Carboxypeptidase B, Pancreatic- 45, 47, 46, 48, like Proteins
 49, 51, 53 50, 52, 54 .sup. 18a CG57113-01 Ribosomal Protein L29-like 55 56
 Proteins 18b CG57113-02 Ribosomal Protein L29-like 57 58 Proteins 19
 CG57211-01 Metalloproteinase-Disintegrin 59 60 (ADAM30)-like Proteins 20
 CG57222-01 Bone Morphogenetic Protein 11- 61 62 like Proteins .sup. 21a
 CG56477-01 Adrenomedullin Receptor-like 63 64 Protein 21b CG56477-02
 Adrenomedullin Receptor-like 65 66 Protein .sup. 21c CG56477-03
 Adrenomedullin Receptor-like 67 68 Protein .sup. 22a CG57256-01 Protein
 Tyrosine Phosphatase-like 69 70 Proteins 22b CG57256-02 Protein Tyrosine
 Phosphatase-like 71 72 Proteins 23 CG57228-01 Aldo-Keto Reductase Family 7,
 73 74 Member A3 like 24 CG57274-01 Ral Guanine NucleotideExchange 75 76
 Factor 3-like Proteins 25 CG57276-01 Endolyn-like Proteins 77 78 26
 CG57224-01 Arylacetamide Deacetylase-like 79 80 Proteins 27 CG57288-01
 GPCR-like Proteins 81 82 28 CG57213-01 PB39-like Proteins 83 84 29
 CG56990-02 Oxytocin-like Proteins 85 86 .sup. 30a CG57330-01 Thymosin
beta-4-like Proteins 87 88 30b CG57330-03 Beta Thymosin-like Proteins 89 90
 .sup. 30c CG57330-02 Thymosin Beta-4-like Proteins 91 92 31 CG57344-01 Myelin
 P2-like Proteins 93 94 .sup. 32a CG57346-01 Testis Lipid-binding
 Protein-like 95 96 Proteins 32b CG57346-02 Testis Lipid-binding Protein-like
 97 98 Proteins 33 CG57356-01 Intracellular Thrombospondin 99 100 Domain
 Containing Protein-like Protein .sup. 34a CG57258-01 Ornithine
 Decarboxylase-like 101 102 Protein 34b CG57258-02 Ornithine
 Decarboxylase-like 103 104 Protein .sup. 34c CG57258-03 Ornithine
 Decarboxylase-like 105 106 Protein 35 CG57339-01 Short-chain 107 108
 Dehydrogenase/Reductase-like Protein 36 CG57341-01 Short-chain 109 110
 Dehydrogenase/Reductase-like Protein 37 CG57335-01 Protocadherin Beta 3-like
 Protein 111 112

Detail Description Table CWU - DETL (163):

163TABLE 30K BLAST results for NOV30a Gene Index/ Length Identity
 Positives Identifier Protein/Organism (aa) (%) (%) Expect
 gi.vertline.17451239.vertline. similar to 158 37/37 37/37 1e-12
 ref.vertline.XP_070564.1.vertline. ribosomal protein (100%) (100%)
 (XM_070564) L10 (H. sapiens) [Homo sapiens] gi.vertline.2143995.vertline.
 thymosin beta-4 56 31/36 31/36 0.015 pir.vertline..vertline.I52084 precursor
 - rat (86%) (86%) (fragment) gi.vertline.136580.vertline. Thymosin beta-4 (T
 50 31/36 31/36 0.089 sp.vertline.P20065.vertline.TYB4_MOUSE beta 4) (86%)
 (86%) gi.vertline.464974.vertline. Thymosin beta-4 (T 43 31/36 31/36 0.089
 sp.vertline.P34032.vertline.TYB4_RABIT beta 4) (86%) (86%)
 gi.vertline.10946578.vertline. thymosin, beta 4, X 44 31/36 31/36 0.089
 ref.vertline.NP_067253.1.vertline. chromosome; (86%) (86%) (NM_021278)

prothymosin beta 4 [Mus musculus]

Detail Description Table CWU - DETL (164):

164TABLE 30M Domain Analysis of NOV30 gnl
.vertline.Smart.vertline.smart00152, THY, Thymosin beta actin-binding motif.
CD-Length = 37 residues, 97.3% aligned Score = 32.0 bits (71), Expect = 0.009
NOV30: 1 MDEIEKFSKSKLKKTEMQEKNPQPSKEWIEQEKQAG 36 (SEQ ID NO:384)
.vertline..vertline..vertline..vertline. .vertline.
.vertline..vertline..vertline..vertline..vertline.
.vertline..vertline..vertline. .vertline..vertline..vertline..vertline.
.vertline..vertline..vertline..vertline..vertline..vertline. Sbjct: 1
TDEIENFDSENLLKKTETIEKNVLPSEKEDIEQEKQLQ 36 (SEQ ID NO:385)

Detail Description Table CWU - DETL (165):

165TABLE 30N Domain Analysis of NOV30 hmmpfam--search a single seq against
HMM database HSIM file: pfamHMNs Scores for sequence family classification
(score includes all domains) Model Description Score E-value N Thymosin
Thymosin beta-4 family 57.1 3.7e-13 1 (INTERPRO) Parsed for domains: Model
Domain seq-f seq-t hmm-f hmm-t score E-value Thymosin 1/1 1 36 [1 41 []
57.1 3.7e-13 Alignments of top-scoring domains: Thymosin: domain 1 of 1,
from 1 to 36: score 57.1, E =3.7e-13
->sDKPdleEiasFDKaKLKKtEtqEKnpLPtKEtiEqEKqae<> (SEQ ID NO: 386)
++..vertline..vertline..++..vertline. .vertline.+..vertline..vert-
line..vertline..vertline..vertline..vertline. .vertline..vertline..vertlin-
e..vertline..vertline.+..vertline.+..vertline..vertline.+..vertline..vertline-
..vertline..vertline..vertline..vertline..vertline.+ NOV30a 1
-----MDEIEKFSKSKLKKTEMQEKNPQPSKEWIEQEKQAG 36 (SEQ ID NO:387)

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ABSTRACT:

Disclosed herein are novel human nucleic acid sequences that have homology to thymosin, ephrin A receptors, proteoglycans and fibromodulin. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving these novel nucleic acids and proteins.

RELATED APPLICATIONS

[0001] This application is a Continuation-in-part of U.S. Ser. No. 09/689,486 filed Oct. 12, 2000 and U.S. Ser. No. 09/687,276 filed Oct. 13, 2000, both of which claim priority to U.S. Ser. No. 60/159,805, filed Oct. 15, 1999, abandoned; U.S. Ser. No. 60/159,992, filed Oct. 18, 1999, abandoned; U.S. Ser. No. 60/086,423, filed Oct. 18, 1999, abandoned; and U.S. Ser. No.

60/160,952 filed Oct. 22, 1999, abandoned. The contents of these applications are incorporated herein by reference in their entireties.

----- KWIC -----

Abstract Paragraph - ABTX (1):

Disclosed herein are novel human nucleic acid sequences that have homology to thymosin, ephrin A receptors, proteoglycans and fibromodulin. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving these novel nucleic acids and proteins.

Summary of Invention Paragraph - BSTX (3):

[0003] Beta-thymosins are a family of related peptides that were first isolated from calf thymus, but are known to be present in a wide variety of mammalian and other vertebrate cells and tissues. Thymosin-beta-4 (TMSB4) was the first member of the family to be characterized, and was proposed to be a thymic hormone acting at early stages of T-cell maturation. However, the high concentration of the protein and presence of its mRNA in a number of other tissues and cells, in addition to the lack of an identifiable secretory signal sequence, suggested a more generalized function in many cell types. This was confirmed by findings that TMSB4 forms a 1:1 complex with G-actin in blood platelets (A. Weber et al., "Interaction of thymosin beta 4 with muscle and platelet actin: implications for actin sequestration in resting platelets," 31(27) Biochemistry 6179-85 (1992)).

Summary of Invention Paragraph - BSTX (4):

[0004] Thymosin-beta-10 is related closely to TMSB4 in sequence and is also an actin-sequestering protein. mRNA species of similar molecular weights encoding TMSB10 are found in most tissues of rats, although Lin and Morrison-Bogorad (1991) identified TMSB10 mRNA of higher molecular weight in the testes of sexually mature rats. The latter differs from the more ubiquitous form only in its 5'-untranslated region, beginning 14 nucleotides upstream of the translation initiation codon. This finding, together with primer extension experiments, suggested that the two mRNA types are transcribed from the same gene through a combination of differential promoter utilization and alternative splicing. Both mRNAs are found in pachytene spermatocytes; only testes-specific mRNA is detected in postmeiotic haploid spermatids. Immunohistochemical analysis shows that the protein was present in differentiating spermatids, which suggests that testes-specific TMSB10 mRNA is translated in haploid male germ cells. Immunoblot analysis using specific antibodies indicates that TMSB10 synthesized in adult testes is identical in size to that made in the brain (S. C. Lin et al., "Cloning and characterization of a testis-specific thymosin beta 10 cDNA. Expression in post-meiotic male germ cells," 266(34) J. Biol. Chem. 23347-53 (1991)).

Summary of Invention Paragraph - BSTX (9):

[0008] In one aspect, the invention provides an isolated NOV1 nucleic acid molecule encoding a NOV1 polypeptide that has identity to the polypeptide sequence for the small actin-sequestering peptide thymosin-beta-10. In another aspect, the invention provides an isolated NOV2 nucleic acid molecule encoding a NOV2 polypeptide that has identity to ephrin type-A receptor 8. In yet another aspect, the invention provides an isolated NOV3 nucleic acid molecule encoding a NOV3 polypeptide that has homology to a family of proteoglycans. In still another aspect, the invention provides an isolated NOV4 nucleic acid

molecule encoding a NOV4 polypeptide that has identity to mature extracellular ephrin type-A receptor 8. In still another aspect, the invention provides an isolated NOV5 nucleic acid molecule encoding a NOV5 polypeptide that has homology to the proteoglycan, fibromodulin.

Detail Description Paragraph - DETX (4):

[0027] For example, NOV1 is homologous to members of the thymosin beta 10 family of proteins. As a result, NOV1 has various marker utilities as described herein. Also, NOV1 has efficacy in treatment of conditions involving development, differentiation, and activation of thymic immune cells; in pathologies related to spermatogenesis and male infertility; diagnosis of several human neoplasias; in diseases or pathologies of cells in blood circulation such as red blood cells and platelets; and detection of small cell lung cancer.

Detail Description Paragraph - DETX (8):

[0031] A NOV1 nucleic acid sequence according to the invention includes nucleic acids encoding a polypeptide related to the small actin-sequestering peptide thymosin-beta-10. An example of this nucleic acid and its encoded polypeptide is presented in Table 1. The disclosed nucleic acid (SEQ ID NO: 1) is 430 nucleotides in length and contains an open reading frame (ORF) that begins with an ATG initiation codon at nucleotides 61-63 and ends with a TAG stop codon at nucleotides 235-237.

Detail Description Paragraph - DETX (9):

[0032] The representative ORF includes a 58 amino acid polypeptide (SEQ ID NO: 2) and is flanked by putative upstream and downstream untranslated regions that are underlined in Table 1. The encoded polypeptide has a high degree of homology (approximately 85 percent identity) with thymosin beta 10 from human (Table 2). A search of the PROSITE database of protein families and domains confirmed that a NOV1 polypeptide is a member of the thymosin beta family, which is defined by polypeptides containing a stretch of 11 highly conserved amino acid residues

Detail Description Paragraph - DETX (11):

[0034] located in the central part of the thymosin beta proteins (Table 2). The PROSITE database consists of biologically significant sites, patterns and profiles that help to reliably identify to which known protein family a new sequence belongs.

Detail Description Paragraph - DETX (12):

[0035] Furthermore, a search of the PFAM database reveals that a NOV1 polypeptide conforms to the sequence profile of thymosin beta family of proteins (Table 3). The query sequence in the table is a NOV1 polypeptide and the subject is a consensus sequence formed from the thymosin beta family of proteins. The presently disclosed NOV1 polypeptide has 84 percent identity across its entire length to the consensus thymosin beta sequence (Table 4). The NOV1 polypeptide bears more homology to the consensus thymosin beta sequence than do many other members of the family. Also, this degree of homology between a NOV1 polypeptide and the thymosin beta consensus (both in terms of length and complexity) is very unlikely to have occurred by chance alone (Expect value in Table 3 less than 1 in 5×10^{10} by chance). Pfam is a large collection of multiple sequence alignments and profile hidden Markov models covering many common protein domain families. It is designed to be both an accurate and comprehensive method to determine homology. A multiple alignment of the thymosin-beta family is presented in Table 3. Based on its relatedness to the thymosin-beta-10 protein, the NOV1 protein is a novel member of the actin-sequestering protein family.

Detail Description Paragraph - DETX (13):

[0036] The thymosin-betas comprise a family of structurally related, highly conserved acidic polypeptides that sequester actin and regulate actin dynamics within cells. During embryogenesis the control of actin polymerization is essential in processes such as cell migration, angiogenesis and neurogenesis. Direct visualization and quantitation of actin filaments has shown that thymosin-betas, like agonists, induced actin depolymerization at the apical membrane where exocytosis occurs (S. Muallem et al., 128(4) J. Cell Biol 589-98 (1995)). Thymosin-beta-10 is widely distributed in mammalian tissues including the nervous system, and the presence of this transcript in different regions of the rat forebrain, including hippocampus, neocortex and several brain nuclei, provides evidence for the participation of thymosin-beta-10 in the control of the actin dynamics that takes place in neurons. Thymosin-beta-10 is expressed at relatively high levels in embryonic and developing tissues (A. K. Hall, 41(3) Cell Mol. Biol. Res. 167-80 (1995)), and given that it is involved in the inhibition of actin polymerization, the thymosin-beta-10 protein-like proteins can play an important role in early development.

Detail Description Paragraph - DETX (14):

[0037] Messenger RNA species of similar molecular weights encoding thymosin beta-10 are found in most tissues of the rat; however, Lin and Morrison-Bogorad identified an additional thymosin-beta-10 mRNA of higher molecular weight in the testis of sexually mature rats (Lin et al., "Cloning and characterization of a testis-specific thymosin beta 10 cDNA. Expression in post-meiotic male germ cells," 266(34) J. Biol. Chem., 23347-53 (1991)). The latter mRNA differs from the ubiquitous form only in its 5-prime untranslated region, beginning 14 nucleotides upstream of the translation initiation codon. This finding, together with primer extension experiments, suggested that the two mRNA types are transcribed from the same gene through a combination of differential promoter utilization and alternative splicing. Both mRNAs were present in pachytene spermatocytes; only the testis-specific mRNA was detected in postmeiotic haploid spermatids. Immunohistochemical analysis showed that the protein was present in differentiating spermatids, suggesting that the testis-specific thymosin-beta-10 mRNA is translated in haploid male germ cells. Immunoblot analysis using specific antibodies showed that the thymosin-beta-10 protein synthesized in adult testis was identical in size to that synthesized in brain.

Detail Description Paragraph - DETX (15):

[0038] Thymosin-beta-10-like proteins also influence several properties of lymphocytes including cyclic nucleotide levels, migration inhibitory factor production, T-dependent antibody production, as well as the expression of various cell surface maturation/differentiation markers (Bodey et al., 22(4) Int. J. Immunopharmacology 261-73 (2000)). These and other observations suggest that thymosin beta-10 (a) plays a significant and possibly obligatory role in cellular processes controlling apoptosis possibly by acting as an actin-mediated tumor suppressor, (b) functions as a neoapoptotic influence during embryogenesis, and (c) can mediate some of the pro-apoptotic anticancer actions of retinoids. Thymosin-beta-10 mRNA is also abundant in a variety of tumors and tumor cell lines.

Detail Description Paragraph - DETX (16):

[0039] Thymosin-beta-10 gene overexpression is a general event in human carcinogenesis. Analysis of thymosin-beta-10 mRNA levels in human colon carcinomas, germ cell tumors of different histological types, breast carcinomas, ovarian carcinomas, uterine carcinomas, colon and esophageal carcinoma cell lines all indicated thymosin-beta-10 was over expressed in all of the neoplastic tissues and cell lines compared to the respective normal tissues. Therefore, detection of thymosin-beta-10-like expression can be

considered a potential tool for the diagnosis of several human neoplasias. (Santelli et al., 155(3) Annals of Am. J. Pathol. 799-804 (1999)). Not only can thymosins like thymosin beta-10 be used for early detection and diagnosis of neoplasms, but also in recent clinical trials derivatives of thymic hormones, mostly of thymosins, have been used to help treat neoplasms (Bodey et al., 22(4) Int. J. Immunopharmacol. 261-73 (2000)). Thymic hormones strengthen the effects of immunomodulators in immunodeficiencies, autoimmune diseases, and neoplastic malignancies. Combined chemo-immunotherapeutical anti-cancer treatment seems to be more efficacious than chemotherapy alone, and the significant hematopoietic toxicity associated with most chemotherapeutical clinical trials can be reduced significantly by the addition of immunotherapy.

Detail Description Paragraph - DETX (17):

[0040] Based on its relatedness to the thymosin-beta-10 protein, the NOV1 protein is a novel member of the actin-sequestering protein family. The discovery of molecules related to thymosin-beta-10 satisfies a need in the art by providing new diagnostic or therapeutic compositions useful in the treatment of disorders associated with alterations in the expression of members of thymosin-beta-10-like proteins. Nucleic acids, polypeptides, antibodies, and other compositions of the present invention are useful in a variety of diseases and pathologies, including by way of nonlimiting example, those involving development, differentiation and activation of thymic immune cells, pathologies related to spermatogenesis and male infertility, diagnosis of several human neoplasias, and diseases or pathologies of cells in blood circulation such as red blood cells and platelets.

Detail Description Paragraph - DETX (18):

[0041] A NOV1 nucleic acid is useful for detecting specific cell-types. For example a variant splice form of a NOV1 nucleic acid according to the invention can be present in different levels in postmeiotic haploid spermatids. Also, according to the invention the expression of a NOV1 nucleic acid has utility in identifying developing and embryonic tissues from other tissue types. Thymosin-beta-10 mRNA is overexpressed in a variety of tumors and tumor cell lines. Expression levels of thymosin-beta-10 like nucleic acids such as NOV1 are also useful in distinguishing T cell types given that expression of various cell surface/differentiation markers is influenced by thymosin-beta-10 like proteins such as a NOV1 polypeptide. A NOV1 nucleic acid has enhanced expression in certain cancer cell lines, especially non-small cell lung cancer NCI-H23, but not in cell lines from the corresponding normal tissue; therefore, NOV1 nucleic acids are useful as a cancer specific marker in such tissues (Example 1).

Detail Description Paragraph - DETX (19):

[0042] Given that thymosin-beta-10 related proteins can sequester actin and regulate actin dynamics within cells, proteins related to the NOV1 polypeptide are useful in screens for test compounds that can modulate actin polymerization or the formation or stability of actin-thymosin beta-10 complexes. Finally, since thymic hormones strengthen the effects of immunomodulators in immunodeficiencies, autoimmune diseases, and neoplastic malignancies, NOV1 related proteins can be used in combined chemo-immunotherapeutical anti-cancer treatments.

Detail Description Paragraph - DETX (20):

[0043] A Representative Amino Acid Sequence of the Thymosin-beta-10-like Protein According to the Invention

Detail Description Table CWU - DETL (1):

1TABLE 1 A representative cDNA sequence encoding the thymosin-beta-10-like protein according to the invention Putative untranslated regions are

underlined. The start and stop codons are in bold type. (SEQ ID NO:1)

GCCAGCAGGAGTGCCATGGTGAGAGGCACTGGCAGGGAATGCTAGGATTGTTTAAAGAAAATGGCAGACA
AAC-
CAGACATAGGGGA AATCGCCAGCTTCAATAAGGCCAAGCTGAAGAAAACAGAGATG-
CAGGAGAACACCCTGCTGACCAAAGAGGCCATTGAGCAGGAGA
AGCGGGTGAAATTTCTAAGAGCCTGGAGGATTCCCTACCCCTGTCATCTTCGAGACCCCAGTAGTAATGT
GG-
AGGAAGAATCACC ACAAGATGGACACAAGCCACAACTGTGACGTGAACCTGGGCAC-
TCCGTGCTGATGCCACCAGCCTGAGGGTCCCTATGGGTCCAA
TCAGACTGCCAAATTCTCTGTTTGCCTGGGATATTATAGAAAATTATTTGCGTGAATAATGAAAACACAG
C-
TCATGGCAAAAAA

Detail Description Table CWU - DETL (2):

2TABLE 2 Comparison between a NOV1 polypeptide and thymosin beta-10 from
human >gb.vertline.AAA36746.1.vertline.(M92383) thymosin beta-10 [Homo
sapiens] Length=49 Score=84.5 bits (192), Expect=3e-16 Identities=34/40
(85%) , Positives 36/40 (90%) , Gaps=1/40 (2%) NOV1: 1
MADKPDIGEIASFNKAKLKKTEMQE-NTLLTKEAIEQEK 39 (SEQ ID NO: 2)
.vertline..vertline..vertline..vertline..vertline..vertlin-
e.+vertline..vertline..vertline..vertline..vertline..vertline.+vertline.-
.vertline..vertline..vertline..vertline..vertline..vertline..vertlin-
e..vertline..vertline..vertline..vertline..vertline..vertline. Sbjct: 6
MADKPDIGEIASFDKAKLKKKTETQEKNLPTKETIEQEK 45 (SEQ ID NO: 34)

Detail Description Table CWU - DETL (3):

3TABLE 4 PFAM alignment of a NOV1 polypeptide to the consensus sequence of
the thymosin beta family >PD005116 (Closest domain: TYB0_HUMAN 1-38)
Number of sequences in family: 16 Most frequent protein names: TYB4(4)
TYB9(2) TYBB(2) Commentary (automatic) THYMOSIN ACETYLATION T-CELL
DIFFERENTIATION IMMUNOPOTENTIATION THYMUS BETA-4 ACTIN-BINDING PROTEIN BETA
Length=38 Score=145 (60.9 bits), Expect=5e-10 Identities=32/38 (84%) ,
Positives =34/38 (89%) , Gaps=1/38 (2%) NOV1: 2
ADKPDIGEIASFNKAKLKKTEMQE-NTLLTKEAIEQEK 38 (SEQ ID NO: 2)
.vertline..vertline..vertline..vertline..vertline.+vertline.-
vertline..vertline..vertline..vertline..vertline.+vertline..vertline..ver-
tline..vertline..vertline..vertline..vertline..vertline..vertlin-
e..vertline..vertline..vertline..vertline..vertline..vertline..v-
ertline..vertline..vertline..vertline. Sbjct: 1
ADKPDIGEIASFDKAKLKKKTETQEKNLPTKETIEQEK 38 (SEQ ID NO: 51)

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ABSTRACT:

Disclosed herein are nucleic acid sequences that encode novel polypeptides. Also disclosed are polypeptides encoded by these nucleic acid sequences, and antibodies, which immunospecifically-bind to the polypeptide, as well as derivatives, variants, mutants, or fragments of the aforementioned polypeptide, polynucleotide, or antibody. The invention further discloses therapeutic, diagnostic and research methods for diagnosis, treatment, and prevention of disorders involving any one of these novel human nucleic acids and proteins.

RELATED APPLICATIONS

[0001] This application is a continuation in part of U.S. Ser. No. 09/540,763, filed Mar. 30, 2000, and claims priority from Applications U.S. Ser. No. 60/206,679, filed May 24, 2000; U.S. Ser. No. 60/206,688, filed May 24, 2000; U.S. Ser. No. 60/206,829, filed May 24, 2000; U.S. Ser. No. 60/207,748, filed May 30, 2000; U.S. Ser. No. 60/207,798, filed May 30, 2000; U.S. Ser. No. 60/208,263, filed May 31, 2000; U.S. Ser. No. 60/208,831, filed Jun. 2, 2000; U.S. Ser. No. 60/209,451, filed Jun. 5, 2000; U.S. Ser. No. 60/210,060, filed Jun. 7, 2000; U.S. Ser. No. 60/219,507 filed Jul. 20, 2000; U.S. Ser. No. 60/221,337, filed Jul. 26, 2000; U.S. Ser. No. 60/221,927, filed Jul. 31, 2000; U.S. Ser. No. 60/263,135, filed Jan. 19, 2001; U.S. Ser. No. 60/263,688, filed Jan. 24, 2001; and 60/263,694, filed Jan. 24, 2001, each of which is incorporated by reference in its entirety.

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Detail Description Paragraph - DETX (40):

[0065] A novel nucleic acid was identified on chromosome 9 by ThlastN using CuraGen Corporation's sequence file for beta thymosin or homolog as run against the Genomic Daily Files made available by GenBank or from files downloaded from the individual sequencing centers. The nucleic acid sequence was predicted from the genomic file GB ACCNO:ba518k17 by homology to a known beta thymosin or homolog. Exons were predicted by homology and the intron/exon boundaries were determined using standard genetic rules. Exons were further selected and refined by means of similarity determination using multiple BLAST (for example, tBlastN, BlastX, and BlastN) searches, and, in some instances, GeneScan and Grail. Expressed sequences from both public and proprietary databases were also added, when available, to further define and complete the gene sequence. The DNA sequence was then manually corrected for apparent inconsistencies thereby obtaining the sequences encoding the full-length protein. In particular, nucleotide 121905 was spliced to nucleotide 121758 in preparing the ba518k17_A sequence.

Detail Description Paragraph - DETX (44):

[0069] The full amino acid sequence of the NOV2a protein of the invention was found to have 33 of 44 amino acid residues (75%) identical to, and 34 of 44 residues (77%) positive with, the 44 amino acid residue Thymosin beta-10 protein from rat (ptnr: PIR-ID:A27266; E=7.2 e-09)(Table 2C). The global

sequence homology is 79% amino acid similarity and 77% amino acid identity. In addition, this protein contains the thymosin protein domain (as defined by Interpro# IPR001152) at amino acid positions 2 to 41. Public amino acid databases include the GenBank databases, SwissProt, PDB and PIR.

Detail Description Paragraph - DETX (60):

[0085] For example, a BLAST against patp:AAR96932, a 43 amino acid synthetic thymosin beta 10 protein (WO96/11016), produced good identity, $E=4.9e-8$. Additionally, a BLAST against patp:AAY80267, a thymosin beta 4 peptide isoform (Theta10) (WO00/06190), a 43 amino acid polypeptide, also produced good identity, $E=4.9e-8$.

Detail Description Paragraph - DETX (61):

[0086] Thymosin-beta-4 (T-beta-4) induces the expression of terminal deoxynucleotidyl transferase activity in vivo and in vitro, inhibits the migration of macrophages, and stimulates the secretion of hypothalamic luteinizing hormone-releasing hormone. Clauss et al. (1991) noted that the protein was originally isolated from a partially purified extract of calf thymus, thymosin fraction 5, which induced differentiation of T cells and was partially effective in some immuno-compromised animals. Further studies demonstrated that the molecule is ubiquitous in all tissues and cell lines analyzed. It is found in highest concentrations in spleen, thymus, lung, and peritoneal macrophages. Li et al. (1996) stated that T-beta-4 is an actin monomer sequestering protein that may have a critical role in modulating the dynamics of actin polymerization and depolymerization in nonmuscle cells. Its regulatory role is consistent with the many examples of transcriptional regulation of T-beta-4 and of tissue-specific expression. Lymphocytes have a unique T-beta-4 transcript relative to the ubiquitous transcript found in many other tissues and cells. In a separate study, Clauss et al. (1991) stated that rat T-beta-4 is synthesized as a 44-amino acid propeptide which is processed into a 43-amino acid peptide by removal of the first methionyl residue and does not have a signal peptide. Comparison studies have shown that human T-beta-4 has a high degree of homology to rat T-beta-4; the coding regions differ by only 9 nucleotides, and these are all silent base changes.

Detail Description Paragraph - DETX (64):

[0089] Bao et al. (1996) found a novel member of the beta thymosin protein family expressed in a metastatic prostate carcinoma cell line. Prostate carcinoma is the most prevalent form of cancer in males and the second leading cause of cancer death among older males. The use of the serum prostate-specific antigen (PSA) test permits early detection of human prostate cancer; however, early detection has not been accompanied by an improvement in determining which tumors may progress to the metastatic stage. The process of tumor metastasis is a multistage event involving local invasion and destruction of extracellular matrix; intravasation into blood vessels, lymphatics or other channels of transport; survival in the circulation; extravasation out of the vessels into the secondary site; and growth in the new location. Common to many components of the metastatic process is the requirement for tumor cell motility. A well-characterized series of cell lines that showed varying metastatic potential was developed from the Dunning rat prostate carcinoma. Mohler et al. (1988) and Partin et al. (1989) showed a direct correlation between cell motility and metastatic potential in the Dunning cell lines. In studies comparing gene expression in poorly and highly motile metastatic cell lines derived from Dunning rat prostate carcinoma using differential mRNA display, Bao et al. (1996) found a novel member of the beta thymosin family of actin-binding molecules, named thymosin-beta-15 (T-beta-15), which was found to deregulate motility in prostate cells directly. In addition, it was expressed in advanced human prostate cancer specimens, but not in normal human prostate or benign prostatic hyperplasia, suggesting its potential use as a new marker

for prostate carcinoma progression. Bao et al. (1996) also found that T-beta-15 levels correlated positively with the Gleason tumor grade. Coffey (1996) pointed out that the upregulation of T-beta-15 as a positive motility factor and the down regulation of the motility suppressor KAI1 provide the 'yin and yang' for metastasis; thus, he speculated that these pathways may provide a new target for therapy.

Detail Description Paragraph - DETX (67):

[0092] The nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to prostate cancer, immunological and autoimmune disorders (i.e. hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen, thymus, lung, and peritoneal macrophages and/or other pathologies and disorders. For example, a cDNA encoding the beta thymosin-like protein may be useful in gene therapy, and the beta thymosin-like protein may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer including but not limited to prostate cancer, immunological and autoimmune disorders (ie hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen, thymus, lung, and peritoneal macrophages. The novel nucleic acid encoding beta thymosin-like protein, and the beta thymosin-like protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

Detail Description Table CWU - DETL (8):

8TABLE 2C BLASTX results for NOV2a Smallest Sum Sequences producing High-scoring Reading High Prob. Segment Pairs: Frame Score P (N) N ptnr: PR-ID: A27266 thymosin beta- +3 137 7.2e-09 1 10 - rat

Detail Description Table CWU - DETL (11):

11TABLE 2F BLASTX results for NOV2b Smallest Sum Reading High Prob. Sequences producing High-scoring Segment Pairs: Frame Score P (N) N ptnr: PIR-ID: A27266 thymosin beta-10 - rat +3 137 1.8e-08 1 ptnr: SWISSPROT-ACC: P13472 THYMOSIN BETA-10 - Homo sapi ... +3 132 6.0e-08 1 ptnr: TREMBLNEW-ACC: BAA96493 THYMOSIN BETA B - Cyprinus ... +3 115 3.8e-06 1 ptnr: SWISSPROT-ACC: P21752 THYMOSIN BETA-9 AND BETA-8 - ... +3 114 4.9e-06 1 ptnr: SPTREMBL-ACC: Q9PT32 THYMOSIN BETA - Oncorhynchus ... +3 113 6.2e-06 1 ptnr: TREMBLNEW-ACC: CAB76965 PUTATIVE THYMOSIN BETA-10 ... +3 113 6.2e-06 1 ptnr: SWISSPROT-ACC: P21753 THYMOSIN BETA-9 - Sus scrofa ... +3 112 7.9e-06 1 ptnr: SWISSPROT-ACC: P26351 THYMOSIN BETA-11 - Oncorhynch ... +3 108 2.1e-05 1 ptnr: PIR-ID: S21282 thymosin beta-11 - rainbow trout +3 108 2.1e-05 1 ptnr: SPTREMBL-ACC: 076538 THYMOSIN BETA - Strongylocent ... +3 107 2.7e-05 1 ptnr: PIR-ID: A59005 thymosin beta - sea urchin (Arbacia ... +3 106 3.4e-05 1 ptnr: PIR-ID: JQ1489 thymosin beta-4 - African clawed frog +3 104 5.6e-05 1 ptnr: PIR-ID: B59005 thymosin beta - scallop (Argopecten ... +3 103 7.1e-05 1 ptnr: SPTREMBL-ACC: Q9W7M8 BETA-THYMOSIN - Brachydanio r ... +3 102 9.1e-05 1 ptnr: SWISSPROT-ACC: P26352 THYMOSIN BETA-12 - Oncorhynch ... +3 101 0.00012 1 ptnr: PIR-ID: S22426 thymosin beta-12 - rainbow trout +3 101 0.00012 1 ptnr: TREMBLNEW-ACC: CAB94229 DJ1071L10.1 (THYMOSIN/INTE ... +3 100 0.00015 1 ptnr: SWISSPROT-ACC: P20065 THYMOSIN BETA-4 - Mus muscul ... +3 99 0.00019 1

Detail Description Table CWU - DETL (15):

15TABLE 2J BLASTX results for NOV2c Smallest Sum Reading High Prob.
Sequences producing High-scoring Segment Pairs: Frame Score P (N) N ptrn:
PIR-ID: A27266 thymosin beta-10 - rat +3 137 1.7e-08 1 ptrn: SWISSPROT-ACC:
P13472 THYMOSIN BETA-10 - Homo sapi . . . +3 132 5.9e-08 1 ptrn:
TREMBLNEW-ACC: BAA96493 THYMOSIN BETA B - Cyprinus . . . +3 115 3.7e-06 1
ptrn: SWISSPROT-ACC: P21752 THYMOSIN BETA-9 AND BETA-8 - . . . +3 114 4.8e-06
1 ptrn: SPTREMBL-ACC: Q9PT32 THYMOSIN BETA - Oncorhynchus . . +3 113 6.1e-06
1 ptrn: TREMBLNEW-ACC: CAB76965 PUTATIVE THYMOSIN BETA-10 . . . +3 113
6.1e-06 1 ptrn: SWISSPROT-ACC: P21753 THYMOSIN BETA-9 - Sus scrofa . . . +3
112 7.8e-06 1 ptrn: SWISSPROT-ACC: P26351 THYMOSIN BETA-11 - Oncorhync . . .
+3 108 2.1e-05 1 ptrn: PIR-ID: S21282 thymosin beta-11 - rainbow trout +3 108
2.1e-05 1 ptrn: SPTREMBL-ACC: 076538 THYMOSIN BETA - Strongylocent . . . +3
107 2.6e-05 1 ptrn: PIR-ID: A59005 thymosin beta - sea urchin (Arbacia . . .
+3 106 3.4e-05 1 ptrn: PIR-ID: JQ1489 thymosin beta-4 - African clawed frog +3
104 5.5e-05 1 ptrn: PIR-ID: B59005 thymosin beta - scallop (Argopecten . . .
+3 103 7.0e-05 1 ptrn: SPTREMBL-ACC: Q9W7M8 BETA-THYMOSIN - Brachydanio r . .
. +3 102 8.9e-05 1 ptrn: SWISSPROT-ACC: P26352 THYMOSIN BETA-12 - Oncorhync .
. . +3 101 0.00011 1 ptrn: PIR-ID: S22426 thymosin beta-12 - rainbow trout +3
101 0.00011 1 ptrn: TREMBLNEW-ACC: CAB94229 DJ1071L10.1 (THYMOSIN/INTE . . .
+3 100 0.00015 1 ptrn: SWISSPROT-ACC: P20065 THYMOSIN BETA-4 - Mus muscul . .
. +3 99 0.00019 1 ptrn: TREMBLNEW-ACC: AAC52490 THYMOSIN B4 - Mus musculus .
. . +3 99 0.00019 1

Detail Description Table CWU - DETL (17):

17TABLE 2N Patp alignments of NOV2 Smallest Sum Sequences producing
High-scoring Reading High Prob. Segment Pairs: Frame Score P (N) Patp:
AAR96932 Thymosin beta 10 - +3 132 4.9e-8 synthetic, 43 aa Patp: AAY80267
Thymosin beta 4 pep- +3 132 4.9e-8 tide isoform, 43 aa

PGPUB-DOCUMENT-NUMBER: 20030180808

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030180808 A1

TITLE: Drug signatures

PUBLICATION-DATE: September 25, 2003

INVENTOR-INFORMATION:

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Natsoulis, Georges	Kensington	CA	US	

APPL-NO: 10/ 378002

DATE FILED: February 28, 2003

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60360728 20020228 US

US-CL-CURRENT: 435/7.1, 435/6 , 435/7.2 , 702/19

ABSTRACT:

Methods for deriving and using Group Signatures and Drug Signatures are provided, wherein Group Signatures comprise a plurality of genes, modulated expression of which is characteristic and specific of a group of related drug compounds, and wherein Drug Signatures comprise a plurality of genes, modulated expression of which is characteristic and specific for individual drug compounds.

[0001] This application claims the benefit of U.S. Provisional Application No. 60/360,728, filed Feb. 28, 2002.

----- KWIC -----

Summary of Invention Paragraph - BSTX (25):

[0023] Another aspect of the invention is a polynucleotide probe set for detecting gemfibrozil-like activity, the set comprising: a plurality of polynucleotides capable of hybridizing specifically to genes selected from the group consisting of Rat fatty acid synthase, Rat cholesterol 7.alpha.-hydroxylase, Mouse acetyl-CoA synthetase, Mouse Vanin-1, Rat kidney-specific protein (KS), Rat 2,3-oxidosqualene:lanosterol cyclase, Rat aldehyde dehydrogenase, and Rat thymosin .beta.-10.

Detail Description Table CWU - DETL (2):

2 Clone ID Gene 700532842 Unknown 700290539 Rat fatty acid synthase mRNA, complete cds 701581809 Incyte EST 701436793 Rat cholesterol 7.alpha.-hydroxylase gene, exon 6 700183232 Mouse acetyl-CoA synthetase mRNA, complete cds 700933512 Mouse mRNA for Vanin-1 700304757 Rat kidney-specific protein (KS) mRNA, complete cds 701228305 Rat mRNA for 2,3-oxidosqualene:lanosterol cyclase, complete cds 701521645 Rat aldehyde dehydrogenase mRNA, complete cds 701562834 Rat thymosin .beta.-10 gene, complete cds

Detail Description Table CWU - DETL (4):

X53477 700304380 Rat p450Md mRNA for cytochrome P450 U15566 701560684 Mouse Tbx2 mRNA, complete cds D90038 700288719 Rat liver 70-kDa peroxisomal membrane protein (PMP70) mRNA AF202115 701463794 Rat GPI-anchored ceruloplasmin mRNA, complete cds S78221 700606373 nuclear protein TIF1 isoform (Mouse, mRNA, 4053 nt) #N/A 700138684 Mouse L-CaBP2 (Cabp2) mRNA, complete cds X53725 700329424 Rat MASH-1 mRNA expressed in neuronal precursor cells (mammalian achaete-scute homologue) U40397 700938882 Mouse serum amyloid A-4 protein (Saa4) gene, complete cds M23995 701521645 Rat aldehyde dehydrogenase mRNA, complete cds 0 700931483 Incyte EST D28566 701192728 Hamster mRNA for carboxylesterase precursor, complete cds M13590 700147294 Rat glutathione S-transferase Yb2 subunit mRNA, 3' end AAF09483 701644022 E2IG4 0 700515449 Incyte EST AB002558 700626043 Rat mRNA for glycerol 3-phosphate dehydrogenase, complete cds AJ302031 700503842 Rat liver regeneration-related protein 1 mRNA, complete cds D16479 700397284 Rat mRNA for mitochondrial long-chain 3-ketoacyl-CoA thiolase .beta.-subunit of mitochondrial trifunctional protein, complete cds AE000664 700503071 Mouse T-cell receptor .alpha. locus BAC clone MBAC519 from 14D1-D2, complete sequence AB010428 700146486 Rat mRNA for acyl-CoA hydrolase, complete cds AF117887 700245634 Mouse protein arginine methyltransferase (Carm1) mRNA, complete cds U43285 700368469 Mouse selenophosphate synthetase 2 mRNA, complete cds U42719 701438090 Rat C4 complement protein mRNA, partial cds AAA65642 700502628 apolipoprotein F S83247 700233325 DA11 = 15.2 kDa fatty acid binding protein/FABP/C-FAPB homolog (rats, Sprague-Dawley, sciatic nerve traumatized, dorsal root ganglia, mRNA Partial, 695 nt) AAA36986 700608519 glutathione S-transferase subunit pi M59189 701436793 Rat cholesterol 7.alpha.-hydroxylase gene, exon 6 0 701644979 Incyte EST AF116897 701193378 Mouse mahogany protein mRNA, complete cds M80427 700303313 Syrian golden hamster androgen-dependent expressed protein mRNA, complete cds M14201 700487123 Rat 11-Kd diazepam binding inhibitor (DBI), partial cds D88250 700372447 Rat mRNA for serine protease, complete cds #N/A 700063031 Rat VL30 element mRNA D37920 700491942 Rat mRNA for squalene epoxidase, complete cds U61266 700522707 Rat Rho-associated kinase .beta. mRNA, complete cds U02553 700187524 Rat protein tyrosine phosphatase mRNA, complete cds AF062389 700304757 Rat kidney-specific protein (KS) mRNA, complete cds D50559 700513027 Rat mRNA for RANP-1, complete cds K02422 701193624 Rat cytochrome P450d methylcholanthrene-inducible gene, complete cds X05684 701559151 Rat L-PK gene for L-type pyruvate kinase M11709 701345507 Rat L-type pyruvate kinase mRNA, complete cds M20131 700502447 Rat cytochrome P450IIE1 gene, complete cds X07266 700492544 Rat mRNA for gene 33 polypeptide V01222 701431070 Messenger RNA for rat prealbumin J04632 700484528 Mouse glutathione S-transferase class .mu. (GST1-1) mRNA, complete cds J05430 701487679 Rat cholesterol 7.alpha.-hydroxylase (CYP7) mRNA, complete cds M77003 700331551 Mouse glycerol-3-phosphate acyltransferase mRNA, complete cds J03734 701194460 Rat Kupffer cell receptor mRNA, complete cds Z50051 700610324 R. norvegicus mRNA for Bovine C4BP .alpha.-chain protein 0 701437076 Incyte EST D90005 701430626 Rat endogenous retroviral sequence, 5' and 3' LTR BAB14526 701826510 oxidoreductase UCPA U38419 700609878 Rat dopa/tyrosine sulfotransferase mRNA, complete cds AF110477 701482962 Rat liver aldehyde oxidase female form (AOX1) mRNA, complete cds S74802 700178702 Rat beta-globin gene, exons 1-3 M34561 700146495 Rat 70 kd heat-shock-like protein mRNA, complete cds 0 701440048 Incyte EST X05341 700228787 Rat mRNA for 3-oxoacyl-CoA thiolase AF172276 701649184 Mouse aldehyde oxidase homolog-1 (Aoh1) mRNA, complete cds AF044574 701246587 Rat putative peroxisomal 2,4-dienoyl-CoA reductase (DCR- AKL) mRNA, complete cds D90109 700527892 Rat mRNA for long-chain acyl-CoA synthetase (EC 6.2.1.3) #N/A 700137495 Rat pcRC201 mRNA for pre-pro-complement C3 X03430 700484501 Rat mRNA for L-type pyruvate kinase AF216873 700183232 Mouse acetyl-CoA

synthetase mRNA, complete cds M58404 701562834 Rat thymosin .beta.-10 gene,
 complete cds M12516 700304405 Rat NADPH-cytochrome P450 reductase mRNA,
 complete cds 0 700501620 Incyte EST K03252 700481289 Rat prealbumin
 (transthyretin) mRNA, complete cds X52984 700609873 Rat mRNA for
 alpha(1)-inhibitor 3, variant I 0 700930555 Incyte EST 0 700328880 Incyte
 EST Z32548 701430793 Mouse TRGC78 DNA 414 bp 0 701518575 Incyte EST
 BAA34502 700180621 KIAA0782 protein U49071 700304375 Rat complement component
 C9 precursor mRNA, partial cds AB012276 700528176 Mouse mRNA for ATFx,
 partial cds AB010632 700480022 Rat mRNA for carboxylesterase precursor,
 complete cds 0 700483266 Incyte EST J02861 701193056 Rat polymorphic,
 male-specific cytochrome P450g mRNA, complete cds AF200357 701258381 Mouse
 pantothenate kinase 1.beta. (panK1.beta.) mRNA, complete cds. D45252
 701228305 Rat mRNA for 2,3-oxidosqualene: lanosterol cyclase, complete cds
 D17370 700307241 Rat mRNA for cystathionine gamma-lyase, complete cds M17083
 700293050 Rat major alpha-globin mRNA, complete cds

Claims Text - CLTX (87):

86. A polynucleotide probe set for detecting gemfibrozil-like activity, the
 set comprising: a plurality of polynucleotides capable of hybridizing
 specifically to genes selected from the group consisting of Rat fatty acid
 synthase, Rat cholesterol 7.alpha.-hydroxylase, Mouse acetyl-CoA synthetase,
 Mouse Vanin-1, Rat kidney-specific protein (KS), Rat
 2,3-oxidosqualene:lanosterol cyclase, Rat aldehyde dehydrogenase, and Rat
thymosin .beta.-10.

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DOCUMENT-IDENTIFIER: US 20030139358 A1

TITLE: Novel human proteins, polynucleotides encoding them and
methods of using the same

PUBLICATION-DATE: July 24, 2003

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RELATED-US-APPL-DATA:

non-provisional-of-provisional 60201951 20000505 US
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non-provisional-of-provisional 60203109 20000508 US
non-provisional-of-provisional 60203295 20000511 US
non-provisional-of-provisional 60210055 20000607 US
non-provisional-of-provisional 60204064 20000512 US
non-provisional-of-provisional 60204063 20000512 US
non-provisional-of-provisional 60204062 20000512 US
non-provisional-of-provisional 60203838 20000512 US
non-provisional-of-provisional 60203839 20000512 US
non-provisional-of-provisional 60204089 20000515 US
non-provisional-of-provisional 60204276 20000516 US

US-CL-CURRENT: 514/44, 435/183, 435/320.1, 435/6, 435/69.1, 435/7.1
, 514/12, 536/23.2

ABSTRACT:

The invention provides polypeptides, designated herein as POLYX polypeptides, as well as polynucleotides encoding POLYX polypeptides, and antibodies that immunospecifically-bind to POLYX polypeptide or polynucleotide, or derivatives, variants, mutants, or fragments thereof. The invention additionally provides methods in which the POLYX polypeptide, polynucleotide, and antibody are used in the detection, prevention, and treatment of a broad range of pathological states.

RELATED APPLICATIONS

[0001] This application claims priority to U.S. No. 60/201,951(21402-001), filed May 5, 2000; No. 60/215,857 (21402-001A), filed Jul. 3, 2000; No. 60/265,162 (21402-001B), filed Jan. 30, 2001; No. 60/203,109 (21402-002), filed May 8, 2000; No. 60/203,295 (21402-003), filed May 11, 2000; No. 60/210,055 (21402-003A), filed Jun. 7, 2000; No. 60/204,064 (21402-004), filed May 12, 2000; No. 60/204,063 (21402-005), filed May 12, 2000; No. 60/204,062 (21402-006), filed May 12, 2000; No. 60/203,838 (21402-007) filed May 12, 2000; No. 60/203,839 (21402-008), filed May 12, 2000; No. 60/204,089 (21402-009), filed May 15, 2000; and No. 60/204,276 (21402-010), filed May 16, 2000. The contents of these applications are incorporated by reference in their entirety.

----- KWIC -----

Summary of Invention Paragraph - BSTX (7):

[0006] The beta thymosin family of proteins and polypeptides induce the expression of terminal deoxynucleotidyl transferase activity in vivo and in vitro, inhibit the migration of macrophages, and stimulate the secretion of hypothalamic leuteinizing hormone-releasing hormone. Thymosin-beta-4, a member of the beta thymosin family has been shown to be a potent wound healing factor. Beta thymosin proteins have also been found to be useful in potential therapeutic applications implicated in cancers, immunological and autoimmune disorders, angiogenesis, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders and other pathological disorders.

Summary of Invention Paragraph - BSTX (93):

[0090] The beta-thymosins are a family of related peptides, initially isolated from calf thymus but known to be present in a wide variety of mammalian and other vertebrate cells and tissues. Thymosin-beta-4 was the first member of the family to be characterized. Although TMSB4 was initially proposed to be a thymic hormone acting at early stages of T-cell maturation, the high concentration of the protein and its mRNA in a number of other tissues and cells, as well as the lack of an identifiable secretory signal sequence, suggested that it had a general function in many cell types. This was confirmed by the demonstration that TMSB4 forms a 1:1 complex with G-actin in blood platelets and other evidence that it is the only known G-actin-sequestering protein present at high enough levels in blood platelets to account for the high levels of G-actin in those cells. Thymosin-beta-4 induces the expression of terminal deoxynucleotidyl transferase activity in vivo and in vitro, inhibits the migration of macrophages, and stimulates the secretion of hypothalamic luteinizing hormone-releasing hormone. The protein was originally isolated from a partially purified extract of calf thymus, thymosin fraction 5, which induced differentiation of T cells and was partially effective in some immunocompromised animals.

Summary of Invention Paragraph - BSTX (94):

[0091] Further studies demonstrated that the molecule is ubiquitous; it had been found in all tissues and cell lines analyzed. It is found in highest concentrations in spleen, thymus, lung, and peritoneal macrophages. Thymosin-beta-4 is an actin monomer sequestering protein that may have a critical role in modulating the dynamics of actin polymerization and depolymerization in nonmuscle cells. Its regulatory role is consistent with the many examples of transcriptional regulation of T-beta-4 and of tissue-specific expression. Lymphocytes have a unique T-beta-4 transcript relative to the ubiquitous transcript found in many other tissues and cells. Rat thymosin-beta-4 is synthesized as a 44-amino acid propeptide which is processed into a 43-amino acid peptide by removal of the first methionyl residue. The molecule does not have a signal peptide. Human thymosin-beta-4 has a high degree of homology to rat thymosin-beta-4; the coding regions differ by only 9 nucleotides, and these are all silent base changes.

Summary of Invention Paragraph - BSTX (95):

[0092] Prostate carcinoma is the most prevalent form of cancer in males and the second leading cause of cancer death among older males. The use of the serum prostate-specific antigen (PSA) test permits early detection of human prostate cancer; however, early detection has not been accompanied by an improvement in determining which tumors may progress to the metastatic stage. The process of tumor metastasis is a multistage event involving local invasion and destruction of extracellular matrix; intravasation into blood vessels, lymphatics or other channels of transport; survival in the circulation; extravasation out of the vessels into the secondary site; and growth in the new location. Common to many components of the metastatic process is the requirement for tumor cell motility. A well-characterized series of cell lines that showed varying metastatic potential was developed from the Dunning rat prostate carcinoma. There is a direct correlation between cell motility and metastatic potential in the Dunning cell lines. In studies comparing gene expression in poorly and highly motile metastatic cell lines derived from Dunning rat prostate carcinoma using differential mRNA display, a novel member of the thymosin-beta family of actin-binding molecules was found (see OMIM-300159). The molecule, named thymosin-beta-15 by them, was found to deregulate motility in prostate cells directly. In addition, it was expressed in advanced human prostate cancer specimens, but not in normal human prostate or benign prostatic hyperplasia, suggesting its potential use as a new marker for prostate carcinoma progression. Thymosin-beta-15 levels correlated positively with the Gleason tumor grade. Upregulation of thymosin-beta-15 as a positive motility factor and the down regulation of the motility suppressor KAI1 (OMIM-600623) provide the 'yin and yang' for metastasis; he speculated that these pathways may provide a new target for therapy.

Summary of Invention Paragraph - BSTX (97):

[0094] The POLY7-8 nucleic acids and proteins of the invention are useful in potential therapeutic applications implicated in cancer including but not limited to prostate cancer, immunological and autoimmune disorders (ie hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen, thymus, lung, and peritoneal macrophages and/or other pathologies and disorders. For example, a cDNA encoding the beta thymosin-like polypeptide may be useful in gene therapy, and the beta thymosin-like polypeptide may be useful when administered to a subject in need thereof. By way of nonlimiting example, the compositions of the present invention will have efficacy for treatment of patients suffering from cancer including but not limited to prostate cancer, immunological and autoimmune disorders (ie hyperthyroidism), angiogenesis and wound healing, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders, and other pathological disorders involving spleen,

thymus, lung, and peritoneal macrophages. The novel nucleic acid encoding beta thymosin-like polypeptide, and the beta thymosin-like polypeptide of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind immunospecifically to the novel substances of the invention for use in therapeutic or diagnostic methods.

Summary of Invention Paragraph - BSTX (101):

[0098] In a search of sequence databases, it was found, for example, that the nucleic acid sequence (SEQ ID NO:13) has 118 of 142 bases (83%) identical to a human beta thymosin mRNA (GENBANK-ID: HUMTHYB4.vertline.ac : M17733). The amino acid sequence of the protein of the invention was found to have 35 of 43 amino acid residues (81%) identical to, and 36 of 43 residues (83%) positive with, the 43 amino acid residue thymosin beta 4 protein from Homo sapiens (ptnr: SWISSPROT-ACC:P01253) (Table 8C). The global sequence homology is 84% amino acid similarity and 81% amino acid identity. In addition, this protein contains the thymosin protein domain (as defined by Interpro# IPR001152) at amino acid positions 9 to 49.

Summary of Invention Paragraph - BSTX (108):

[0105] In a search of sequence databases, it was found, for example, that the nucleic acid sequence (SEQ ID NO:15) has 145 of 166 bases (87%) identical to a human beta thymosin mRNA (GENBANK-ID: D82345.vertline.acc:D82345). The full amino acid sequence of the protein of the invention was found to have 35 of 40 amino acid residues (87%) identical to, and 36 of 40 residues (90%) positive with, the 45 amino acid residue thymosin beta protein from Homo sapiens (ptnr: PIR-ID:JC5274) (Table 9C). The global sequence homology is 81% amino acid similarity and 80% amino acid identity. In addition, this protein contains the thymosin protein domain (as defined by Interpro# IPR001152) at amino acid positions 21 to 60.

Summary of Invention Paragraph - BSTX (112):

[0109] Thymosin-beta-4, a member of the beta thymosin family has been shown to be a potent wound healing factor. Beta thymosin proteins have also been found to be useful in potential therapeutic applications implicated in cancers, immunological and autoimmune disorders, angiogenesis, modulation of apoptosis, neurodegenerative and neuropsychiatric disorders, age-related disorders and other pathological disorders. Therefore, POLY7-8 are useful to identify novel beta thymosin-binding protein family members.

Summary of Invention - Table CWU - BSTL (28):

28TABLE 8C BLASTX identity search against HEMATOPOIETIC SYSTEM REGULATORY PEPTIDE--Homo sapiens (Human) (SEQ ID NO: 35) >ptnr:SWISSPROT-ACC:P01253 THYMOSIN BETA-4 (FX) [CONTAINS: HEMATOPOTETIC SYSTEM REGULATORY PEPTIDE]--Homo sapiens (Human), Bos taurus (Bovine),, 43 aa. Length = 43 Plus Strand HSPs: Score = 173 (60.9 bits), Expect = 1.3e-12, P = 1.3e-12 Identities = 35/43 (81%), Positives = 36/43 (83%), Frame = +3 Query: 27 SDPPDFASLPKRDKSKLKKTEVQKKNPLPSKEMIEQEKQAGES 155 (SEQ ID NO.14) .vertline..vertline..vertline..vertline..vertline.. + .vertline. .vertline..vertline..vertline..vertline..vertline..vertline..vertline..ve- rtline..vertline..vertline..vertline..vertline..vertline..vertline..vertl- ine..vertline..vertline..vertline..vertline..vertline..vertline..vertline- ..vertline..vertline..vertline..vertline..vertline..vertline..vertline. Sbjct: 1 SDKPDMAEIEKFDKSKLKKKTETQKKNPLPSKETIEQEKQAGES 43 (SEQ ID NO:35) Other polypeptide sequence with homology to POLY7 are indicated in Table 8D.

Summary of Invention - Table CWU - BSTL (29):

29TABLE 8D Smallest Sum Reading High Probability Sequences producing

High-scoring Segment Pairs: Frame Score P(N) N patp:AAY76578 Human ovarian tumor EST fragment encoded. . . -2 181 3.2e-13 1 patp:AAP81169 Protein produced in myeloma cell differe. . . +3 173 2.2e-12 1 patp:AAR04593 Thbeta4-tumour necrosis factor fusion pe. . . +3 173 2.2e-12 1 patp:AAR96921 Thymosin beta 4--Synthetic, 43 aa. +3 173 2.2e-12 1 patp:AAW81507 Thymosin beta 4, X isoform (TB4X) gene p. . . +3 173 2.2e-12 1

Summary of Invention: Table CWS-037E (52):
32)TABLE 9C BLASTX IDENTITY SEARCH AGAINST THYMOSIN BETA - HUMAN (SEQ ID NO:36)
 <gt;pntnr:PIR-ID:JC5274 **thymosin beta** - human Length = 45 Plus Strand
 HSPs: Score = 161 (56.7 bits), Expect = 2.4e-11, P = 2.4e-11 Identities = 35/40 (87%), Positives = 36/40 (90%), Frame = +1 Query: 61
 MSDKPNLSEV-KFDRSKLKKTNTGEKNRLSSKETIQQEKE 177
 .vertline..vertline..vertline..vertline..vertline.+..vertline.-
 .vertline..vertline..vertline. .vertline..vertline..vertline..vertline..ver-
 tline..vertline..vertline..vertline..vertline..vertline..vertline..vertlin- e.
 .vertline..vertline..vertline. vertline. vertline..vertline..vertline-
 ..vertline..vertline..vertline..vertline..vertline..vertline..vertline. Sbjct:
 1 MSDKPDLSEVEKFDRSKLKKTNTEEKNTLP SKETIQQEKE 40 (SEQ ID NO:36)

Summary of Invention, Table C-9, SEQ ID NO. 9.

TABLE 9D Smallest Sum Probabilistic Reading High ty Sequences producing High-scoring Segment Pairs:

Frame Score	P(N)	N	patp:AAP81169 Protein produced in myeloma cell differe.
+1 167	9.7e-12	1	patp:AAW14281 Human neuroblastoma-specific thymosin-be.
+1 161	4.2e-11	1	patp:AAW81508 Thymosin beta 4, Y isoform (TB4Y) gene p.
+1 159	6.8e-11	1	patp:AAW81507 Thymosin beta 4, X isoform (TB4X) gene p.
+1 158	8.7e-11	1	patp:AAB53712 Human colon cancer antigen protein seque.
+1 158	8.7e-11	1	patp:AAY91956 Human cytoskeleton associated protein 11.
+1 158	8.7e-11	1	patp:AAW46486 Human thymosin beta-15 protein - Homo sa.
+1 156	1.4e-10	1	patp:AAW36056 Human thymosin beta-15 protein sequence.
+1 154	2.3e-10	1	patp:AAW68573 Rat thymosin-beta15 protein - Rattus sp..
+1 154	2.3e-10	1	patp:AAW44275 Human thymosin beta 15 - Homo sapiens, 4.

46-**TABLE 12E** Smallest Sum Reading High Probability Sequences producing
High-Scoring Segment Pairs: Frame Score P(N) N patp:AAP81169 Protein produced
in myeloma cell differe ... +1 167 9.7e-12 1 patp:AAW14281 Human
neuroblastoma-specific thymosin-be ... +1 161 4.2e-11 1 patp:AAWB1508
Thymosin beta 4, Y isoform (TB4Y) gene p ... +1 159 6.8e-11 1 patp:AAW81507
Thymosin beta 4, X isoform (TB4X) gene p ... +1 158 8.7e-11 1 patp:AAB53712
Human colon cancer antigen protein seque ... +1 158 8.7e-11 1 patp:AAV91956
Human cytoskeleton associated protein 11 ... +1 158 8.7e-11 1 patp:AAW46486
Human thymosin beta-15 protein - Homo sa ... +1 156 1.4e-10 1 patp:AAW36056
Human thymosin beta-15 protein sequence ... +1 154 2.3e-10 1 patp:AAW68573
Rat thymosin-beta15 protein - Rattus sp, ... +1 154 2.3e-10 1 patp:AAW44275
Human thymosin beta 15 - Homo sapiens, 4 ... +1 154 2.3e-10 1

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TITLE: Compositions comprising mixtures of therapeutic proteins and methods of producing the same

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INVENTOR-INFORMATION:

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Wan, Winnie H.	Woodside	CA	US	
Browning, Laura	Brentwood	CA	US	
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US-CL-CURRENT: 424/85.5, 424/85.6 , 424/85.7

ABSTRACT:

Human cytokine mixtures produced by cytokine regulatory factor-overexpressing cells and methods of production are disclosed. The mixtures are prepared by culturing human cytokine-producing cells under conditions of cytokine regulatory factor overexpression, treating the cells to induce cytokine production, and isolating the mixtures of cytokines produced by the cells. Preferred compositions, for use in treating viral infection or cancer, include a mixture of human interferon .gamma. and either human interferon .alpha. or human interferon .beta., in a mole ratio of between 2:1 to 1:100 interferon .gamma. to interferon .alpha. or human interferon .beta..

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/660,468, filed Sep. 11, 2000, U.S. patent application Ser. No. 09/952,843, filed Sep. 11, 2001, and U.S. patent application Ser. No. 10/105,100, filed Mar. 21, 2002, all of which are incorporated herein in their entirety by reference.

----- KWIC -----

Detail Description Table CWU - DETL (4):

4TABLE 4 Results of Gene Chip expression of A9 (PKR-transfected) Namalwa cells following induction Protein Avg Diff Description of Protein Apoptosis-1,218 Cluster including AF022385: Homo sapiens related apoptosis-related protein TFAR15 protein (TFAR15) mRNA BMP 11 513.9 Cluster including AF100907: Homo sapiens bone morphogenetic protein 11 (BMP11) mRNA Caspase-like 1,390 AF005775 Homo sapiens caspase-like apoptosis apoptosis regulatory protein 2 (clarp) mRNA, regulatory alternatively spliced protein 2 CD27 18,475 Cluster including M63928: Homo sapiens T cell activation antigen (CD27) mRNA CD27L 17,166 Cluster including L08096: Human CD27 ligand mRNA Chemokine 3,006 D43767 = HUMAR Human mRNA for chemokine Chemokine 611.5 Cluster including U86358: Human (TECK) chemokine (TECK) mRNA Death do- 795 U84388 = HSU84388 Human death domain main con- containing protein CRADD mRNA taining prot CRADD EGF 813 X04571 = HSEGFRR Human mRNA for kidney epidermal growth factor (EGF) precursor FGF 18 309 Cluster including AF075292: Homo sapiens fibroblast growth factor 18 (FGF18) mRNA Gastrin-223 K02054/FEATURE = mRNA/ releasing DEFINITION = HUMGRP5E Human peptide gastrin-releasing peptide mRNA, complete cds GH-1/GH-2/ 9,416 Cluster including J03071: Human growth CS-1/CS-2 hormone (GH-1 and GH-2) and chorionic somatomammotropin (CS-1, CS-2 and CS-5) genes Heat shock 2,313 Cluster including M64673: Human heat shock factor 1 factor 1 (TCF5) mRNA Heat shock 1655.3 M64673 = HUMHSF1 Human heat shock factor 1 factor 1 (TCF5) mRNA Heat shock 567 Cluster including M65217: Human heat shock factor 2 factor 2 (HSF2) mRNA Hepatoma- 2,910 Cluster including D16431: Human mRNA for derived hepatoma-derived growth factor growth factor HGF-like 684 Cluster including U28055: Homo sapiens protein hepatocyte growth factor-like protein homolog mRNA HSP 70 21,120 Heat Shock Protein, 70 Kda HSP 70 11,072 Heat Shock Protein, 70 Kda HSP 70 858 L12723 = HUMHSP70H Human heat shock protein 70 (hsp70) mRNA HSP 70B 508 X51757/FEATURE = cds/DEFINITION = HSP70B Human heat-shock protein HSP70B gene HSP 90 16,057 Cluster including M16660: Human 90-kDa heat-shock protein gene HSP 90 13,458 Cluster including X15183: Human mRNA for 90-kDa heat-shock protein HSP E 2238.2 Cluster including L08069: Human heat shock protein, E. coli IFN-a 9,344 M28585 = HUMIFNN Human leukocyte interferon-alpha mRNA IFN-a 8,053 J00207 = HUMIFNAA Human leukocyte interferon (leif) alpha-a gene IFN-a a 2817.8 J00207 = HUMIFNAA Human leukocyte interferon (leif) alpha-a gene IFN-a 2,019 Cluster including V00541: Messenger RNA for human leukocyte interferon IFN-a d 9,300 J00210 = HUMIFNAD Human leukocyte interferon (IFN-alpha) alpha-d gene IFN-a5 2,522 X02956 = HSIFNA5 Human interferon alpha gene IFN-alpha 5 IFN-a6 1345.6 X02958 = HSIFNA6 Human interferon alpha gene IFN-alpha 6 IFN-a-M1 6,154 M27318 = HUMIFNAM1 Human interferon (IFN-alpha-M1) mRNA IFN-b 8,284 V00535 = HSIFD6 Gene for human fibroblast interferon beta 1 IFN-g 6,263 Cluster including L07633: Homo sapiens interferon-gamma IEF SSP 5111 mRNA IFN-g 152 Cluster including X13274: Human mRNA for interferon IFN-gamma IFN-omega 2,356 Cluster including X58822: Human IFN-omega 1 gene for interferon-omega 1 IGF-II 1,217 M13970 = HUMGFI21 Human insulin-like growth factor (IGE-II) gene, exon 1 of 4 IL-1b 291 Cluster including M15330: Human interleukin 1-beta (IL1B) IL-1R2 1,522 X59770 = HSIL1R2II H. sapiens IL-1R2 mRNA for type II interleukin-1 receptor IL-1ra 1,816 Cluster including X52015: H. sapiens mRNA for interleukin-1 receptor antagonist IL-3 171 M20137 = HUMIL3A Human interleukin 3 (IL-3) mRNA IL-4 349 M13982 = HUMIL4 Human interleukin 4 (IL-4) mRNA Inhibitor of 11,479 U45878 = HSU45878 Human inhibitor of apoptosis apoptosis protein 1 mRNA protein 1 Lipocortin 2 13253.2 Cluster including M62895: Human lipocortin (LIP) 2 pseudogene mRNA Lipocortin II 11,053 D00017 = HUMLIC Homo sapiens mRNA for lipocortin II Macrophage- 5,397 Cluster including U83171: Human derived macrophage-derived chemokine precursor

chemokine (MDC) mRNA MIF 21,100 L19686 = HUMMIF Homo sapiens macrophage migration inhibitory factor (MIF) gene Monocyte- 1,520 Cluster including U49020: Human specific myocyte-specific enhancer factor 2A enhancer (MEF2A) gene factor Myelin-assoc 334 Cluster including D28113: Human mRNA for oligoden. MOBP (myelin-associated oligodendrocytic basic prot basic protein) Myocyte- 1520.2 Cluster including U49020: Human specific myocyte-specific enhancer factor 2A enhancer (MEF2A) gene factor NK 2,529 Cluster including L19185: Human natural killer enhancing cell enhancing factor (NKEFB) mRNA factor Oral tumor 4923.8 Cluster including AF006484: Homo sapiens suppressor putative oral tumor suppressor protein protein (doc-1) mRNA (doc-1) Osteogenic 2356.6 Cluster including X51801: Human OP-1 protein mRNA for osteogenic protein PK inhibitor 158.4 Cluster including S76965: protein kinase inhibitor [human, neuroblastoma cell line SH-SY-5Y PK inhibitor 846.1 Cluster including AB019517: Homo sapiens gamma PKIG mRNA for protein kinase inhibitor gamma PKCI-1 12,528 U51004 = HSU51004 Homo sapiens protein kinase C inhibitor (PKCI-1) Pre-B cell 733 Cluster including U02020: Human pre-B enhancing cell enhancing factor (PBEF) mRNA factor Prothymosin 5,279 Cluster including M14630: Human alpha prothymosin alpha mRNA RANTES 22,392 M21121 = HUMTCSM Human T cell-specific protein (RANTES) mRNA RANTES 11,265 M21121 /FEATURE = /DEFINITION = HUMTCSM Human T cell-specific protein (RANTES) mRNA RANTES 1464.2 M21121 = HUMTCSM Human T cell-specific protein (RANTES) mRNA SOD3 848 J02947 = HUMSODEC Human extracellular- superoxide dismutase (SOD3) mRNA sVEGF R 645 U01134 = U01134 Human soluble vascular (sflt) endothelial cell growth factor receptor (sflt) mRNA TGF-b 3,899 M38449 = HUMTGFB Human transforming growth factor-beta mRNA Thymosin 17,132 Cluster including M92383: Homo sapiens beta-10 thymosin beta-10 gene Thymosin 19,683 Cluster including M17733: Human thymosin beta-4 beta-4 mRNA Thymosin 915 Cluster including AF000989: Homo sapiens beta 4 thymosin beta 4 Y isoform (TB4Y) mRNA TNF/LT 1,392 M16441 = HUMTNFAB Human tumor necrosis factor and lymphotoxin genes TNF/LT 933 M16441 = HUMTNFAB Human tumor necrosis factor and lymphotoxin genes TNF-b 5,506 Cluster including D12614: Human mRNA for lymphotoxin (TNF-beta) TRAIL 6878.2 U37518 = HSU37518 Human TNF-related apoptosis inducing ligand TRAIL mRNA TRAMP 5,480 Cluster including X63679: H. sapiens mRNA for TRAMP

US-PAT-NO: 6602519

DOCUMENT-IDENTIFIER: US 6602519 B1

TITLE: Oxidized thymosin .beta.4

DATE-ISSUED: August 5, 2003

INVENTOR-INFORMATION:

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GB	9806632	March 28, 1998

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102(E)-DATE:

US-CL-CURRENT: 424/451, 424/422 , 424/434 , 424/435 , 424/436 , 424/464
, 424/489 , 514/12 , 514/2

ABSTRACT:

The present invention relates to the use of oxidized thymosin .beta.4 in therapy, more particularly in the treatment of diseases or conditions associated with an inflammatory response of septic shock.

4 Claims, 20 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 14

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Brief Summary Text - BSTX (19):

Thymosin .beta.4 in an oxidised or non-oxidised form may be obtained from any suitable source, for example from steroid treated monocytes. Moreover, the thymosin .beta.4 may be derived from any suitable species, but is typically of mammalian origin, such as bovine, equine, murine or human origin. It is to be noted that bovine, equine, murine, rat and human thymosin .beta.4 are all identical in sequence. Thus, for example, bovine thymosin .beta.4 may provide a suitable source of thymosin .beta.4 for subsequent oxidation and

administration to other species, such as humans.

Brief Summary Text - BSTX (26):

According to the present invention there is also provided a synthetic oxidised thymosin .beta.4 comprising the peptide sequence of thymosin .beta.4 in oxidised form or physiologically active variant thereof.

Brief Summary Text - BSTX (33):

The invention further provides use of a nucleotide molecule having a sequence capable of encoding thymosin .beta.4 as described herein for subsequently preparing oxidised thymosin .beta.4.

Detailed Description Text - DETX (69):

Note: Cannot distinguish between Leu and Ile [LI] as they are isomers.
Sequences corresponded exactly to tryptic fragments of human Thymosin Beta-4.